STUDY OF PREVALENCE OF THYROID DYSFUNCTION IN SEROPOSITIVE HIV PATIENTS

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BONAFIDE CERTIFICATE

This is to certify that the dissertation titled **"A STUDY ON PREVALANCE OF THYROID DYSFUNCTION IN SEROPOSITIVE HIV PATIENTS"** submitted by **Dr. A. PRABHU** to the Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfilment of the requirement for the award of M.D Degree Branch I (General Medicine) is a bonafide research work and it was carried out by him under my direct supervision & guidance.

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This is to certify that this dissertation titled **"A STUDY ON PREVALANCE OF THYROID DYSFUNCTION IN SEROPOSITIVE HIV PATIENTS" is** the bonafide work of DR **A. PRABHU,** in partial fulfilment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for **M.D General Medicine Branch I** examination to be held in **April 2015.**

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DECLARATION

I, **Dr. A. PRABHU** solemnly declare that, I carried out this dissertation titled, **"A STUDY ON PREVALANCE OF THYROID DYSFUNCTION IN SEROPOSITIVE HIV PATIENTS"** at the Department of Medicine, Govt. Rajaji Hospital during the period of JUNE 2014 to SEPTEMBER 2014. I also declare that this bonafide work or a part of this work was not submitted by me or any others for any award, degree, and diploma to any other University, Board either in India or abroad.

This is submitted to **The Tamilnadu Dr. M.G.R. Medical University, Chennai,** in partial fulfilment of the rules and regulations for the M.D degree examination in General Medicine.

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ABSTRACT

INTRODUCTION:

Several endocrinopathies have been reported to be associated with HIV infection when the CD4 count is low. So before the advent of HAART, subclinical and clinical thyroid, adrenal and gonadal disturbances have been identified[1.]

An abnormal thyroid function test results are seen among human immunodeficiency virus (HIV) infected patients and is caused by various mechanisms such as infiltration of the gland by opportunistic infections or a systemic manifestation of the infection itself. This causes subclinical Hypothyroidism[4] which is a precursor to overt hypothyroidism.

Subclinical hypothyroidism is associated with only mild clinical abnormalities and is characterised by normal T4 values but with elevation in thyroid-stimulating hormone (TSH).Specific thyroid function test abnormalities are identified among HIV-infected patients. But the incidence of overt thyroid illness is same as that of the general populationAmong the HIV patients:

Overt thyroid disease 1-2%

Subtle abnormalities in thyroid function test [5, 6, and 7] 35%

Thyroid abnormalities in HIV-infected patients are dealt in detail in this study.

AIMS AND OBJECTIVES OF THE STUDY:

To evaluate patients with human immunodeficiency virus (HIV) infection for the prevalence of thyroid dysfunction and to correlate the results with the CD4 count.

MATERIALS AND METHODS:

STUDY POPULATION:

This study is to be conducted among 50 patients with Seropositive HIV, attending the Department of Medicine & ART Centre in Govt. Rajaji Hospital, Madurai.

STUDY PROTOCOL:

In Patients of HIV Positive on ART, both sex, T3, T4, TSH, CD4 Count are done .Results are then analysed

RESULTS:

People with CD4 count between 100- 200 were having a mean TSH value of 8.45+/-0.32 and people with CD4 less than <100 were having TSH values 9.75+/-0.39 (p= <.001) and there is no significant correlation between thyroid dysfunction and patients on HAART

CONCLUSIONS:

Thyroid dysfunction is found in significant association with HIV infection and a hypothyroid state occurs in HIV infection as the disease progresses. Males and females suffering from HIV show equal incidence of thyroid dysfunction.

All individuals with CD4 count less than 200 should be screened for hypothyroidism. In individuals with a low CD4 count, a lower BMI is observed as compared to other patients with CD4 counts higher than them. There is no significant correlation between thyroid dysfunction and patients treated with HAART.

KEY WORDS: Thyroid dysfunction, Thyroid function test, HIV, HAART, CD4 Count,

INTRODUCTION

Several endocrinopathies have been reported to be associated with HIV infection when the CD4 count is low. So before the advent of HAART, subclinical and clinical thyroid, adrenal and gonadal disturbances have been identified[1.]

An abnormal thyroid function test results are seen among human immunodeficiency virus (HIV) infected patients and is caused by various mechanisms such as infiltration of the gland by opportunistic infections or a systemic manifestation of the infection itself. This causes subclinical Hypothyroidism[4] which is a precursor to overt hypothyroidism.

Subclinical hypothyroidism is associated with only mild clinical abnormalities and is characterised by normal T4 values but with elevation in thyroid-stimulating hormone (TSH).

Euthyroid sick syndrome (i.e. non thyroidal illness) is more common in HIV patients with advanced disease. Specific thyroid function test abnormalities are identified among HIV-infected patients. But the incidence of overt thyroid illness is same as that of the general population. During HAART therapy, many patients screened had an elevated thyroid-stimulating hormone levels and decreased free thyroxin levels.

In immune reconstitution syndrome the exact opposite occurs. It is characterised by Graves' disease with low TSH and increased thyroxin levels. Routine thyroid screening of asymptomatic HIV infected individuals is not recommended. But testing of symptomatic patients should begin with measurement of the TSH level.

This review highlights the current evidence regarding the optimal evaluation of thyroid function test and discusses the controversies of routine screening.

Among the HIV patients:

Overt thyroid disease 1-2%

Subtle abnormalities in thyroid function test [5, 6, and 7] 35%

The physician must interpret abnormal thyroid function test with the above results in mind. The diagnosis, treatment and interpretation of thyroid function tests in HIV-infected patients are reviewed and the indications for screening are formulated. Current concepts in thyroid dysfunction in HIV patients, in contrast to the general population with a broader context for thyroid abnormalities in HIV-infected patients are dealt in detail in this study.

AIMS AND OBJECTIVES OF THE STUDY

- To evaluate patients with human immunodeficiency virus (HIV) infection for the prevalence of thyroid dysfunction.
- To correlate the results with the CD4 count

REVIEW OF LITERATURE

HISTORY:

Hypothyroidism is a clinical syndrome which was described for the first time in London in 1870. It was named myxedema. In 1888 it was accepted widely that cretinism myxedema and post thyroidectomy changes were a result of loss of function of thyroid body. Kendall isolated thyroxin for the first time in 1914. Harrington synthesized it for the first time in 1926.However; synthesis of thyroxin was done in large scale in 1949. Later it became a universally accepted therapy for hypothyroidism[8]

THYROID GLAND:

Anatomy of Thyroid:

Thyroid gland comprises of:

- A midline isthmus lying horizontally just below the cricoid cartilage
- Right and left, two lateral lobes that extend superiorly together, in front of neck giving the appearance of a butterfly shape.
- The gland is fully enclosed by pre tracheal fascia, under the strap muscle, which makes the gland move up with deglutition[25].

Histology of thyroid:

- Thyroid gland is divided by Thin fibrous septa into pseuolobules
- These pseudolobules are composed of vesicles otherwise called follicles or acini, are densely surrounded by a capillary network.
- Follicular walls are surrounded by cuboidal epithelium
- Proteinaceous colloidal material is filled within the lumen of follicles which contains the unique protein called thyroglobulin. The peptide sequences of T4 and T3 are stored and synthesized as a component of thyroglobulin.

Development of thyroid:

- Develops from the ectoderm of the floor of the pharynx with some contribution from the lateral pharyngeal pouches.
- The thyroglossal duct, which extends from the foramen caecum near the base of the tongue to the isthmus of the thyroid arise from descent of the midline thyroid anlagen.
- The posterior aspect of the thyroid gland becomes associated with the parathyroid gland and the para follicular C cells, during the development, which are derived from ultimo-bronchial body, which become incorporated in to its substance[25].
- While they undergo malignant transformation, the C cells are the source of the calcitonin and gives rise to medullary thyroid carcinoma.

- At about 10-12 weeks of intra uterine life, the foetal thyroid begins to concentrate and organify iodine.
- Maternal TSH and T4 do not cross the placenta, but the maternal TRH crosses the placenta.
- The major source of thyroid hormone in the foetal life is T4 from the foetal thyroid.
- The functional unit is foetal pituitary- thyroid axis which is distinct from that of mother.

PHYSIOLOGY OF THYROID GLAND:

Thyroid secretes three hormones – thyroxin (T4), triiodothyronine (T3) and calcitonin. Thyroid follicles secrete the first two hormones, have similar biological activity and the term "thyroid hormones" is pertinent to these 2 hormones only. Calcitonin is chemically and biologically different entirely and is secreted from parafollicular C cells. It regulates calcium metabolism and it is considered along with parathormone.

Thyroid hormone contains iodine. Iodine enters the thyroid in the form of inorganic or organic iodide is oxidized by a peroxidase enzyme at the cell-colloidal interface. Subsequent reactions results in formation of thyroxin. The only source of T4 is thyroid gland. Thyroid secretes 20% of T3; extra glandular tissues produce the remaining amount by the peripheral conversion of T4 into T3[25].

CHEMISTRY AND SYNTHESIS OF THYROID HORMONE:

Both T4 and T3, which is a condensation product of 2 molecules of tyrosine are iodine containing derivatives of thyronine.

Thyroxine (T4) - 3, 5, 3', 5'- tetraiodothyronine

T3 - 3, 5, 3' – triiodothyronine

Thyroid hormones are synthesized and stored in thyroid follicles as part of thyroglobulin molecule which is a glycoprotein synthesized in thyroid cells, contains 10% of sugar, MW 660 KDa. There are 5 steps in synthesis of thyroid hormones.

1. **IODIDE UPTAKE OR IODIDE TRAPPING:** Iodine from peripheral circulation is taken into the follicles by active transport process called Na + I- symporter or NIS. Iodine content of follicle regulates the iodide trap. Meager storage activates and large storage inhibits this trap. This process is mediated by TSH. Percholarate, thiocyanates and nitrates inhibits this trapping.
2. **OXIDATION AND IODINATION :**Iodide trapped by follicular cells is transported by one another transporter across the apical membrane called as "pendrin" and oxidized by thyroid peroxidase enzyme present in follicular membrane and forms iodinium ions (I+) or hypoiodous acid (HOI) or enzyme linked hypoiodate (E-OI) with the help of H2O2.

   These various forms of iodine bound avidly with thyroglobulin and forms monoiodotyrosine (MIT) and diiodotyrosine (DIT).

3. **COUPLING:** Pairs of iodinated tyrosine residues forms T3 and T4 by coupling with one another .Coupling belongs to oxidative reaction and is catalysed by the same thyroid peroxidase. Oxidation and coupling, both reactions are regulated by TSH.
4. **STORAGE AND RELEASE:** Tyrosil residues are stored as thyroid colloid. These materials is taken back into follicular cells by endocytosis and undergo lysosomal proteolysis then released as T4 and T3. This colloidal uptake and proteolysis are mediated by TSH. At rest, follicles filled with colloid has flat or cuboidal epithelium and TSH stimulated follicles has columnar cells, colloid emptied.
5. **PERIPHERAL CONVERSION OF T4 TO T3:** Conversion occurs predominantly in kidney and liver. One third of T4 undergoes conversion and most of T3 in plasma is derived from liver. Target organs take up T3 for metabolic functions except brain and pituitary which take up T4 and converts in to T3 by their own cellular mechanisms.

Relation between T3 and T4:

- Normally thyroid secretes more amount of T4 compared to T3. But this difference is reduced in iodine deficient state.
- Normally T4 is the major circulating form because it is avidly bound with plasma proteins 15 times more.
- T3 is five times more potent than T4.

- T3 acts very faster than T4.
- Peak effect of T3 comes earlier (1-2 days), but peak effect of T4 comes later (6-8 days).
- T3 is more tightly bound to the nuclear receptors than T4 and the T4-receptor complex is not able to activate or depress the gene transcription.
- About one third of T4 is converted in to T3 in peripheral tissues, in liver and kidney, by D1 type of 5' Deiodinase (D1type 5'DI) and released in to circulation. But in addition, T3 is generated within the target cells like skeletal muscles, brain, pituitary and heart, by another enzyme type called type 2 deiodinase (D2 type 5'DI). T4 is converted in to metabolically active T3 or inactive reverse T3 (r T3).
- T4 and T3 metabolized in liver by conjugation with glucuronate and sulfate. Enzyme inducers such as phenobarbitone, carbamazepine and phenytoin increase the metabolic clearance of the hormones without decreasing the proportion of free hormones in the circulation.
- Finally, T3 is an active form. T4 is a transport form i.e. precursor of T3.
- Normal daily secretion of T3- 10-30 mcgm. T4- 60-90 mcgm.
- T3 and T4 bound with 3 plasma proteins – they are

i) Thyroxin binding globulin (TBG)

ii) Thyroxin binding pre albumin (Transthyretin)

iii) Albumin

- Plasma t ½ of T3 is 1-2 days; of T4 is 6-7 days. The half life is increased in hypothyroidism and shortened in hyperthyroidism due to enhanced and blunted metabolism respectively.

- Thyroid is the only source of T4.

Circumstances with altered concentration of TBG[25]:

INCREASED TBG	DECREASED TBG
1. New born	1. Phenytoin
2. OCP / Estrogens/Tamoxifen	2.Acromegaly
3. Biliary cirrhosis	3.Androgens
4. HAV/Chronic active hepatitis	4. Nephrotic syndrome
5. Acute intermittent porphyria	5. Large doses of glucocorticoids and Cushing's syndrome
6. Pregnancy	6. Chronic liver disease

REGULATION OF SECRETION:

Thyroid hormone secretion is regulated by hypothalamo-pituitary-thyroid axis. Thyrotropin releasing hormone (TRH) from hypothalamus stimulates anterior pituitary to secrete TSH. This in turn stimulates thyroid gland and thyroxin is released from thyroid follicles. T3 and T4 are then released into circulation. T3 and T4 by the negative feedback mechanism directly control both hypothalamus and anterior pituitary.

Thyrotropin releasing hormone:

This is major positive regulator for pituitary TSH synthesis and release. TRH production starts infetus as early as 30 days of the gestation. It undergoes rapid degradation in the serum. It reaches pituitary by a pathway consisting of TRH fibres that enter median eminence and release TRH into portal system. TRH also reach pituitary by direct diffusion from hypothalamus or through cerebrospinal fluid and sub arachnoid process.

The anterior pituitary:

Anterior lobe contains multiple hormones cell type including cells that produce TSH.TSH cells are thought to be part of the lineage that is dependent on home box transcription factor pit-12. Fetal pituitary TSH synthesis can be detected by 13 weeks but remains low till 18 weeks after which both serum and pituitary TSH levels rise dramatically. This is followed by increase in the serum total and free T4 levels.

TSH Action:

TSH regulates thyroid gland function through TSH-R, a seven-transmembrane G protein–coupled receptor (GPCR). The TSH-R is coupled to the subunit of stimulatory G protein (G), activates adenylyl cyclase, leading to increased production of cyclic AMP. TSH also stimulates phosphatidylinositol turnover by activating phospholipase C. The functional role of TSH-R is exemplified by consequences of naturally occurring mutations. Recessive loss-of-function mutations cause congenital hypothyroidism and thyroid hypoplasia. Dominant gain-of-function mutations cause sporadic or familial hyperthyroidism that is characterized by thyroid cell hyperplasia, goiter and autonomous function.

This mimics the changes induced by TSH covalent binding or the interactions with thyroid-stimulating immunoglobulin's (TSI) in Graves' disease. Activating TSH-R mutations occur as somatic events, leading to clonal selection and expansion of the affected thyroid follicular cell and autonomously functioning thyroid nodules.

Although TSH is the dominant hormonal regulator of thyroid gland growth and function, many growth factors, secreted in the thyroid gland regulates the synthesis of thyroid hormone. They are endothelia, transforming growth factor (TGF),epidermal growth factor and insulin-like growth factor I (IGF-1).

The quantitative roles of these factors are not well understood, but they are important in selected disease states. In Acromegaly, increased levels of growth hormone and IGF-1 are associated with goiter and predisposition to multinodular goiter (MNG).Certain interleukins (ILs) and cytokines produced in association with autoimmune thyroid disease induce thyroid growth, whereas others lead to apoptosis. Iodine deficiency upregulates the NIS. It increases blood flow to thyroid and iodine uptake. Transient inhibition of thyroid iodide organification, by excess iodide itself is called *Wolff-Chaikoff effect*. In individuals with normal thyroid, iodide organification resumes and the gland escapes from this inhibitory effect; the suppressive action of high iodide may persist in patients with underlying autoimmune thyroid disease[10].

CAUSES OF HYPOTHYROIDISM

Primary:

- Subtotal or total thyroidectomy, Iatrogenic treatment, external irradiation of neck for lymphoma.
- Type 3 deoiodinase over expression - infantile hemangioma
- Congenital hypothyroidism: TSHR mutation, dyshormonogenesis, absent or ectopic thyroid gland
- Infiltrative disorders like sarcoidosis, scleroderma, cystinosis, amyloidosis, hemochromatosis, Reidel's thyroiditis

- Autoimmune hypothyroidism: atrophic thyroiditis, Hashimoto's thyroiditis.
- Drugs: sunitinib, iodine excess (including iodine-containing contrast media and amiodarone),antithyroid drugs, interferon, cytokines, aminoglutethimide,lithium and*p*-aminosalicylic acid,
- Deficiency of iodine.

Transient:

- Withdrawal of thyroxine treatment
- Post treatment or subtotal thyroidectomy for Graves' disease
- Subacute thyroiditis
- Silent thyroiditis, including postpartum thyroiditis.

Secondary:

- Hypothalamic disease:Infiltrative disorders, tumors, trauma, idiopathic
- Hypopituitarism: tumors, pituitary surgery / irradiation, or infiltrative disorders
- Isolated TSH inactivity or deficiency
- Genetic forms of combined pituitary hormone deficiencies
- Sheehan's syndrome, trauma
- Bexarotene treatment.

CLINICAL PRESENTATION OF HYPOTHYROID DISORDERS:

Symptoms:

- Feeling cold
- Dry skin
- Tiredness, weakness
- Hair loss

Signs:

- Puffy face, hands, and feet (my edema)
- Constipation
- Diffuse alopecia
- Delayed tendon reflex relaxation
- Weight gain with poor appetite
- Dry coarse skin; cool peripheral extremities
- Serous cavity effusions
- Difficulty in concentrating and poor Memory
- Dyspnoea
- Peripheral edema
- Bradycardia
- Menorrhagia
- Hoarse voice
- Carpal tunnel syndrome

Clinical Examination:

Examination is normal in most of the cases. However some may present with clinical signs such as typical hypothyroid facies suggestive of overt hypothyroidism. Skin maybe cold, dry, rough and scaly. Peripheral edema of feet and hand typically non pitting maybe seen. Nails maybe brittle and thickened.

Some patients can have loss of hair in the lateral third of the eyebrows and scalp .Patients may have sinus bradycardia and diastolic hypertension. Blood pressure maybe normal or low in subclinical hypothyroidism. The thyroid gland may be rubbery, enlarged and firm. It is not tender and no bruit is heard. Thyroid maybe normal in size also. Patients can have memory loss and slow speech. A polyneuropathy or mononeuropathy like carpel tunnel syndrome with involvement of several peripheral nerves with complaints such as parasthesia may be seen in some cases.

LABORATORY EVALUATION:

Measurement of Thyroid Hormones:

The TSH levels change dynamically in response to alterations of T4 and T3. The first approach to thyroid testing is to first find out whether TSH is normal, suppressed or elevated. With very rare exceptions, a normal TSH level excludes a primary abnormality of thyroid function. The enhanced sensitivity

and specificity of *TSH assays* have greatly improved laboratory assessment of thyroid function.

Immune chemiilluminometric assays (ICMAs) for TSH are sensitive enough to discriminate between the suppressed values that occur with thyrotoxicosis and the lower limit of the reference range. Extremely sensitive (fourth-generation) assays can detect TSH levels 0.004 mU/L, but for practical purposes, assays sensitive to 0.1 mU/L are enough. The TRH stimulation test is now obsolete because of the widespread availability of the TSH ICMA. Also there is often a failure of TSH to rise after an intravenous bolus of 200–400 g .

The finding of an abnormal TSH level should then be followed by circulating thyroid hormone levels to correctly diagnose hypothyroidism (elevated TSH) or hyperthyroidism (suppressed TSH). Radio immunoassays are widely available for serum *totalT*4 and *total T*3. T4 and T3 are highly protein-bound. Medications, illness, genetic factors etc. can influence protein binding. So the free or unbound hormone levels, which correspond to the biologically available hormone pool should be measured next.

This is because total thyroid hormone level is not affected by changes in serum binding protein affinity. Serum TSH level is the first line investigation in the diagnosis of primary hypothyroidism and hyperthyroidism. However the test is not diagnostic in secondary thyroid dysfunction.

Thyroid hormones level in various clinical conditions[25]:

CONDITION	FREE T3	FREE T4	TSH
Subclinical hypothyroidism	Increased	Normal	Normal
Subclinical hyperthyroidism	Normal	Normal	Low
Primary hyperthyroidism	Increased	increased	Undetectable
Primary hypothyroidism	Low or normal	Low	High
Secondary hyperthyroidism (TSHoma)	Increased	Increased	Normal /increased
Secondary hypothyroidism	Low or normal	Low	Low or normal
T3 toxicosis	Well increased	normal	undetectable

Drugs influencing metabolism and thyroid hormone function25:

METABOLIC PROCESS	INCREASED	DECREASED
Binding proteins	Heroin, Estrogens, clofibrate	Androgens,Glucocorticoids, phenytoin, Carbamazepine
T4synthesis/ release	Iodine	Lithium, Iodide
T4 / T3 binding in serum		Frusemide, Amiodarone, mefenamic acid, beta blockers, glucocorticoids, Salicylates
T 4 metabolism	Rifampicin Anticonvulsants	
TSH secretion	Amiodarone	Phenytoin, Glucocoticoids, dopamine agonists

THYROID HORMONE RESISTANCE[25]:

This is a syndrome characterized by elevated free T3, free T4 but with normal TSH level. But TSH responsiveness to TRH is normal. Patient may have thyromegaly, short stature, attention deficit, mental retardation and learning difficulty and hyperactivity. The differential diagnosis for this is TSH-secreting pituitary tumour. Treatment is by suppressing TSH with bromocriptine, D T4, tri iodo-thyroacetic acid and octreotide. Thyroid ablation by either radioiodine or surgery is tried if refractory to medical management.

SCREENING FOR THYROID DISEASE[23]:

The following patients should be screened for thyroid illness:

1. Annual TFT for diabetic patients
2. Type 1 DM women in first trimester of pregnancy and post delivery
3. Patients with hyperlipidaemia
4. Monthly assessment in patients on amiodarone and lithium
5. History of post partum thyroiditis
6. Atrial fibrillation patients
7. Annual TFT in Turner' syndrome, Down's syndrome, and Addison's disease,because of high prevalence of hypothyroidism in those patients.

ATYPICAL THYROID FUNCTION TESTS[25]:

TESTS	CAUSE
Detectable TSH , Elevated FT3,FT4	Heterophile antibodies TSH secreting pituitary tumour Thyroid hormone resistance
Low FT3, Elevated FT4	Amiodarone
Normal FT4, Suppressed TSH	T3 toxicosis
Suppressed TSH , Normal FT3,FT4	Excess thyroxine replacement Early subclinical thyrotoxicosis Sick euthyroidism Recovery from thyrotoxicosis

SICK EUTHYROID SYNDROME/ NON THYROIDAL ILLNESS SYNDROME:

- Low T4 and T3 with normal or low TSH
- Low concentration of thyroid hormones in all tissues
- Found in - starvation, severe systemic illness, cardiac failure, liver Failure, infections, malignancy ,adrenal failure
- Benefit of thyroxine replacement is controversial
- Treat the underlying illness.

ATYPICAL CLINICAL SITUATIONS [25]:

***Struma ovarii* :**

Ovarian teratoma with hyperfunctioning thyroid tissue. There is no thyroid enlargement. Diagnosed by body scan after radioiodine.

***Thyrotoxicosis factitia* :**

Without thyroid enlargement, increased free T4 and lowTSH, depressed uptake in scintigraphy. To differentiate it from thyroditis, thyroglobulin level is done which is low.

***Choriocarcinoma of testes* :**

Associated with thyrotoxicosis and gynaecomastia – measure HCG.

***Transient hyperthyroidism of Hyperemesis gravidarum*:**

Increased beta HCG level is the most accepted mechanism. LH, FSH, TSH and beta HCG are glycoprotein hormones. They contain a specific beta subunit and a common alpha subunit. TSH level is decreased and serum free T4 raised. TFT returns to normal after recovery from hyperemesis gravidarum. Anti thyroid drugs need not be initiated.

***Trophoblast tumours* :**

These tumours secrete HCG. This HCG is structurally similar to TSH and eventually stimulates thyroid. So there may be mild thyrotoxicosis.

AMIODARONE AND THYROID FUNCTION[21]:

Amiodarone is a benzofuronic derivative with structural similarity with thyroxin. High concentration of iodine is present in amiodarone (39 % by weight). Daily optimal intake of iodine is around 150 – 200 micro gram. But with a dose of amiodarone between 200 – 700 mg per day, 7 – 21 mg of iodine enters the body. Half life of amiodarone is 52.6 ± 23.7 days.

Thyroid function abnormality occurs in 50 % of patients on chronic amiodarone therapy.

In areas with high iodine intake amiodarone induced hypothyroidism (AIH) develops. Amiodarone induced thyrotoxicosis (AIT) occurs in areas with low iodine intake. AIT develops even after several months of discontinuation of amiodarone due to its long half life. Hypothyroidism is common in females and in patients with positive thyroid auto antibodies. the thyroid function test should be done every 6 months in patients on amiodarone therapy. Thyrotoxicosis due to iodine excess is referred as AIT type I. Thyrotoxicosis due to toxic effect of amiodarone is called as AIT type II.

FEATURE	AIT TYPE I	AIT TYPE II
Etiology	Iodine excess	Thyroiditis
Vascularity (Doppler)	Normal / increased	Decreased
Goiter	Frequent	Infrequent
Thyroid antibodies	Positive	Negative
Late hypothyroidism	No	Possible
Thyroid Clinical signs	Present	Absent
Serum IL 6	Normal	Highly elevated
Thyroglobulin	Normal / mild elevation	Highly elevated
Radioiodine uptake	Normal	Decreased

SUBCLINICAL HYPOTHYROIDISM:

TSH level is raised but free thyroid hormones are normal. Indication for treatment of subclinical hypothyroidism is:

1. TSH level > 10
2. Thyroid auto antibodies positive
3. Previous treatment of grave's disease / radioiodine treatment
4. Pregnancy.

SUBCLINICAL HYPERTHYROIDISM:

Undetectable TSH level and normal levels of T3 and T4. This may be endogenous when associated with nodular thyroid disease or underlying Grave's disease and exogenous when over correction with levothyroxine. In

endogenous type, if patient is older ablative therapy with $I^{131}$is the best initial treatment. In exogenous type, dose of thyroxin has to be reduced except in those with prior thyroid malignancy in whom TSH suppression is mandatory. And if there is new onset cardiac failure, atrial fibrillation, angina, accelerated bone loss or borderline high serum T3 level is present, the dose of levothyroxine must be reduced.

THYROID AND PREGNANCY:

TBG level is increased during pregnancy. Total T3 and T4 levels may be raised but the free hormone levels are normal. Trimester adjusted reference values are to be taken as normal values during pregnancy.

The free T4 index ("adjusted T4") can be taken as a reliable assay during gestational period. The nonpregnant total T4 level (50–150 nmol/liter) can be taken by multiplying this range by 1.5-foldin the second and third trimesters of pregnancy.

SCREENING FOR HYPOTHYROIDISM[11]:

Various recommendations have been proposed.

1. AmericanThyroid Association:

Men and women >35 years must be screened every 5 years

2. American association of clinical endocrinologist:

Women and older people should be screened

3. American college of obstetrics and gynaecology:

Women with autoimmune disease and family history of thyroid disease screened at 19 years

4. American college of Physicians:

Symptomatic thyroid disease in Women>50 years

5. U.S Preventive services task force:

No proper evidence for or against screening

6. Royal College of Physicians:

Healthy adult population is not justified

7. Indian thyroid society:

Routine screening is not indicated.

SCREENING OF HIGH RISK POPULATION[12]:

In this subset of patients routine screening for thyroid dysfunction would be beneficial

1. Menstrual irregularities
2. Infertility
3. Dyslipidemia
4. Unexplained hyponatremia
5. Type 1 diabetes
6. Carpel tunnel syndrome
7. Depression
8. Short stature

9. Recurrent abortion

10. Down's syndrome

11. Pregnancy

12. Family history of thyroid disease

13. Exposure to radiation.

DIAGNOSIS[13]:

TSH estimation is a very effective method to screen thyroid dysfunction. IF TSH levels are elevated T3/T4 estimation should be done. If T3/T4 levels are normal possibility of subclinical hypothyroidism should be considered/ Free T3/T4 estimation maybe done to confirm the diagnosis. Anti TPO antibodies maybe done if Hashimoto thyroiditis is suspected.

TREATMENT[14]:

Treatment of all cases of subclinical hypothyroidism is not generally indicated. Follow up with repeat TSH levels may be required in some cases. There are three principal reasons for starting therapy in subclinical hypothyroidism

1. To avert the symptoms of overt thyroid failure
2. To reverse the effect of mild thyroid failure on various organ systems and relieve subtle signs and symptoms caused by mild thyroid failure
3. In specific situations like:

   a. Positive anti thyroid antibodies

b.Dyslipidemia

c. Pregnancy

d. Infertility

e. Goitre

f. Obesity

g. Carpel tunnel syndrome

h. Menstrual irregularities

i. Unexplained hyponatremia

j. Short stature

Whereas dosage of thyroxin of overt hypothyroidism is 1.6-1.8µg/kg/day, an initial dose of thyroxin of up to 50-75µg per day is sufficient to bring the serum TSH level to normal in patients with subclinical hypothyroidism[15].

A lower dose (12.5-25µg daily)is given to coronary artery disease patients. After four to six weeks of therapy serum TSH is measured to see the response to treatment. It is also done after any change in the dose. Once the levels become stable, follow up TSH measurements are done annually. Thyroxine requirements increase pregnancy[16] as there is a progressive thyroid failure and hence TSH has to be repeated at regular intervals and dose modified accordingly.

GOALS OF THERAPY:

Goal should be to keep the patient's thyroid profile in euthyroid range with optimum dose of thyroxin supplementation. TSH level should be kept in the range of 0.5 to 5.0μIU/ml. In the pregnant TSH should be <2.5μIU/ml. The patient should be followed up regularly till optimal control is achieved.

If the patient had abnormal lipid profile before initiation of the treatment repeat lipid profile once in 3 months till the biochemical parameters normalizes.

COMPLICATIONS OF THERAPY:

1. **Osteoporosis:** Elderly, post-menopausal women are more prone to develop osteoporosis. This complication can be minimized by giving calcium supplements and encouraging calcium rich diet.
2. **Subclinical hyperthyroidism:** This complication can be prevented by regular follow up and dose titration. Initially TSH should be repeated once in 6 weeks later once in 3 months. Once TSH levels stabilizes patient can be followed up once in 6 months and yearly thereafter.
3. **Overt manifestation of Ischemic heart disease:** In those patients with established coronary artery disease is advisable to start with the lowest dose (12.5μ/day) followed by gradual titration according to TSH values. If high dose of thyroxin is initiated at the start of the therapy patient may present with ischemic symptoms.

HIV

HISTORY:

The origin of AIDS dates back to the late 1960s when scientists had no clue about this dreadful disease. A virus that affects the chimpanzees of Africa, known as the SIV (simian immunodeficiency virus) is very similar to the one causing AIDS in humans. It is believed that this deadly virus has spread from the remote parts of Africa to the rest of the world. The first case was reported among gay men known as GRID – gay related immunodeficiency[33] in America in 1981. But later on an investigation of the blood of a bantu tribal man in Belgian Congo in 1959, who was identified to have a mysterious illness revealed the same virus. He was then declared as he first reported confirmed case of AIDS.

Soon a large number of young people were identified with an illness characterised by a near total destruction of their immune system. Centre for Disease Control and Prevention (CDC) identified a large number of cases of pneumocystis carinii pneumonia and Kaposi sarcoma in the same year. This illness causing immunodeficiency and rare opportunistic infections was termed as Acquired Immuno Deficiency Syndrome (AIDS). In Pasteur Institute, France, Luc Montagnier isolated a virus from the lymph node of a patient in 1983 and named it LAV (Lymphadenopathy Associated Virus)[34].In 1984, Dr. Robert Gallo, isolated a virus which he called HTLV- III in the National Cancer Institute, New York . Later both these viruses were found to be the

same. An antibody test to detect the virus called ELISA was developed in 1985. In 1986, the name of the virus was coined as the Human Immunodeficiency Virus (HIV) and the first drug 'zidovudine' was developed against HIV.

"World AIDS Day" was first observed on December 1st 1988. Deaths due to AIDS continued to multiply until the late 1990s. Then a newer treatment regimen was devised called HAART (Highly Active Anti Retroviral Therapy) and it revolutionised the entire treatment of AIDS. More potent drugs like Nevirapine and Saquinavir were discovered which decreased the death rate to a great extent.

GLOBAL AIDS CRISIS:

AIDS continues to be the greatest challenge to modern medicine even today.

AIDS statistics – WORLD 2013

- No. of deaths due to HIV AIDS : 1.7 million (approx)
- No. of people living with HIV AIDS : 35.5 million (approx)
- No. of new infections with HIV : 2.4 million (approx)

AIDS statistics – INDIA 2013

• No. of deaths due to HIV AIDS	:	1.8 lakhs (approx.)
• No. of new infections with HIV	:	1.04 lakhs (approx.)
• No. of people living with HIV AIDS	:	24 lakhs (approx)
• Prevalence of HIV AIDS	:	0.30%

By the HAART regimen, the rate of new infections has fallen by 33% , the death rates have improved significantly but the number of PLHA (people living with HIV and AIDS) is on the rise due to the increased longevity due to the ART. The rate of spread and death toll continue to rise in sub Saharan Africa .

The practical problems in reaching out to the AIDS victims are:

- Unawareness of their HIV status
- Poor access to treatment due to it either lack of resources or lack of initiative
- Low economic status of people of the developing nations
- Social stigma[25,26].

Because of these inequalities 'The AIDS pandemic' has begun to plateau in some nations, while it is still on the rise in some others.

DEFINITION AND CLASSIFICATION[24]:

DEFINITION:

HIV positive person with T lymphocyte CD4+ count of <200 /µL has been termed as AIDS irrespective of associated infections or significant symptoms.

CLASSIFICATION:

The current CDC classification system for HIV patients takes into account, the CD4+ T lymphocyte count and the associated clinical conditions.

CD4+ T cell count (per µL)	**Category A – asymptomatic/ acute HIV/ PGL**	**Category B – symptomatic**	**Category C – AIDS indicators**
>500	A1	B1	C1
200 – 400	A2	B2	C2
<200	A3	B3	C3

Once a patient is designated category B as defined by his present clinical condition and CD4+ T cell count, it cannot be reverted back again to ' category A' regardless of his recovery from the respective condition/ symptoms under category B. Similarly this applies to category C patients reverting back to category B.

CATEGORY A :

Patients with one or more of the following conditions or symptoms, but conditions enumerated under category B or C must not be present.

These include:

- Generalised lymphadenopathy (persistent)
- HIV infection– Asymptomatic
- Acute symptomatic HIV infection (clinical disease or history of acute HIV infection)

CATEGORY B:

Patients with one or more of the following conditions, but those under category C must not be present plus the conditions related to HIV or deficiency in cell mediated immunity.

These include[24]:

- Oral thrush
- Oral hairy leukoplakia
- >1 episode/ >1 dermatome – herpes zoster
- Listeria infection
- Fever/ diarrhoea> 1 month
- Bacillary angiomatosis
- Idiopathic thrombocytopenic pupura

- Vulvovaginal candidiasis (non responsive to routine treatment/ recurrence)
- Cervical dysplasia/ carcinoma in situ
- PID like tubo ovarian mass or abscess
- Peripheral neuropathy

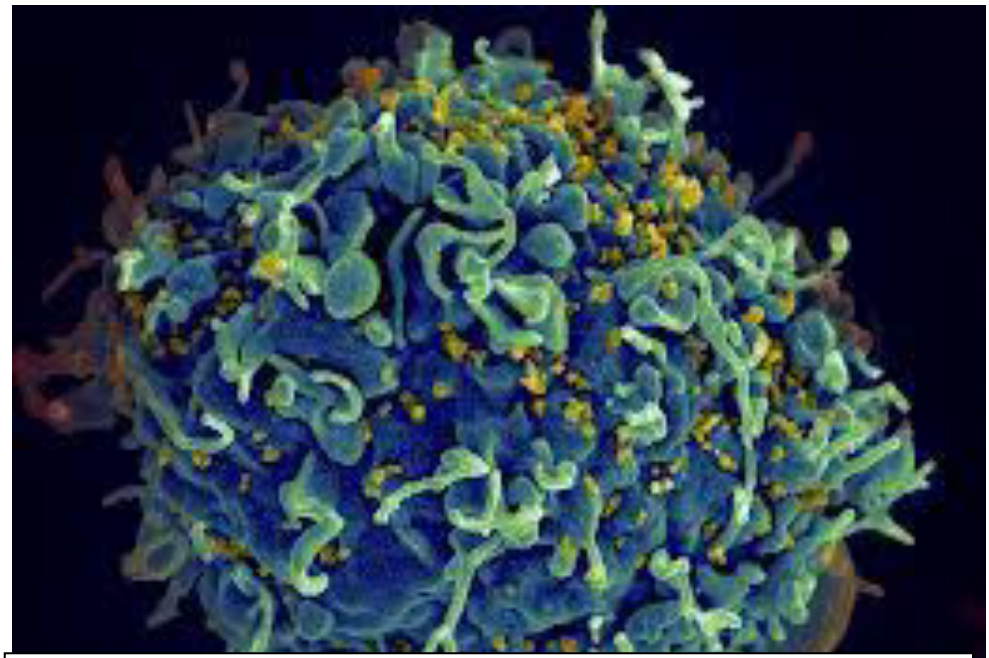
CATEGORY C:

Diseases or infections coined together as **AIDS defining illness**[24]

- Invasive candidiasis (esophagus, trachea, lung or bronchi)
- Pulmonary or extrapulmonary TB
- Histoplasmosis
- Cryptococcosis
- Chronic intestinal Cryptosporidiosis / isospora infection
- CMV retinitis
- Mycobacterium Avium Complex infection
- Herpes simplex infections (bronchitis, pneumonia, esophagitis)
- Coccidioidomycosis
- Pneumocystis carinii pneumonia
- CNS toxoplasmosis
- Recurrent pneumonia/ salmonella sepsis
- Invasive cervical malignanacy

- Kaposi sarcoma
- Primary CNS lymphoma
- Burkitt s lymphoma
- HIV encephalopathy
- AIDS cachexia
- Progressive multifocal leukoencephalopathy (PML)

Figure 1 :THE AIDS VIRUS

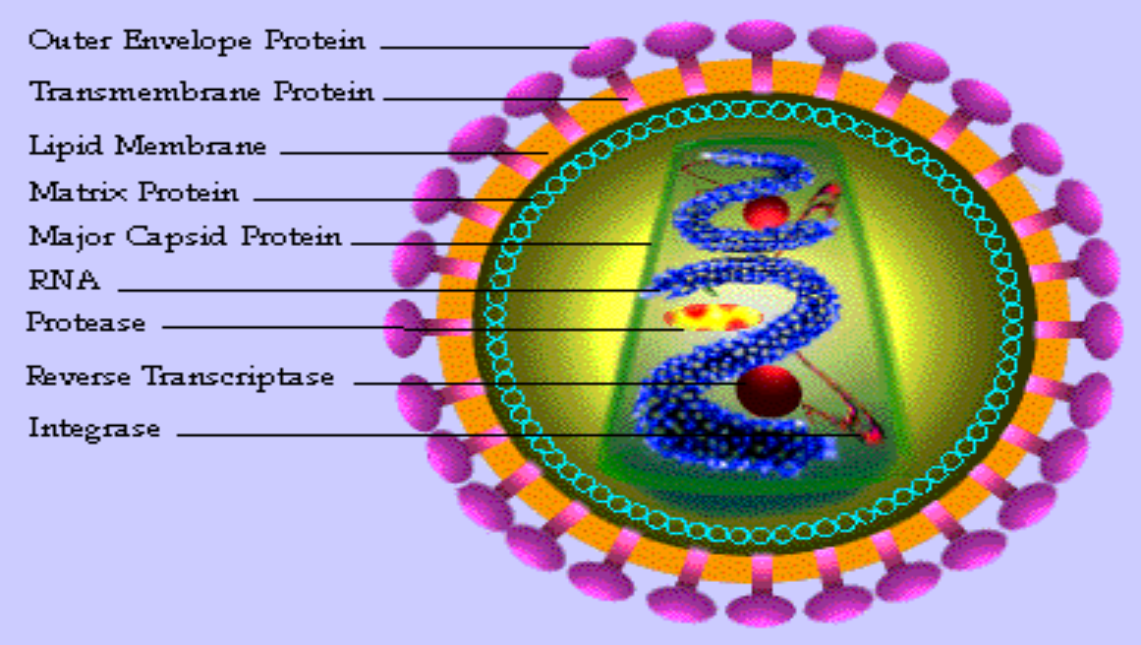


Scanning electron micrograph of HIV-1 virions infecting human CD4+ T lymphocyte

HUMAN IMMUNODEFICIENCY VIRUS - STRUCTURE:

The human immune deficiency virus is classified under the family **retroviridae** and the sub family of **lentiviruses**. There are 2 types of viruses, HIV-1 and HIV-2. HIV- 1 is responsible for the widely spread global pandemic. Whereas HIV-2 isolated from western Africa is sporadic and its distribution is widespread. The virus has an icosahedral structure and has 2 major envelope proteins, a surface protein gp 120 and another transmembrane protein, gp41.Being a retroviruses, HIV-1 has a single-stranded and a plus-sense RNA.

Figure 2: COMPONENTS OF HIV

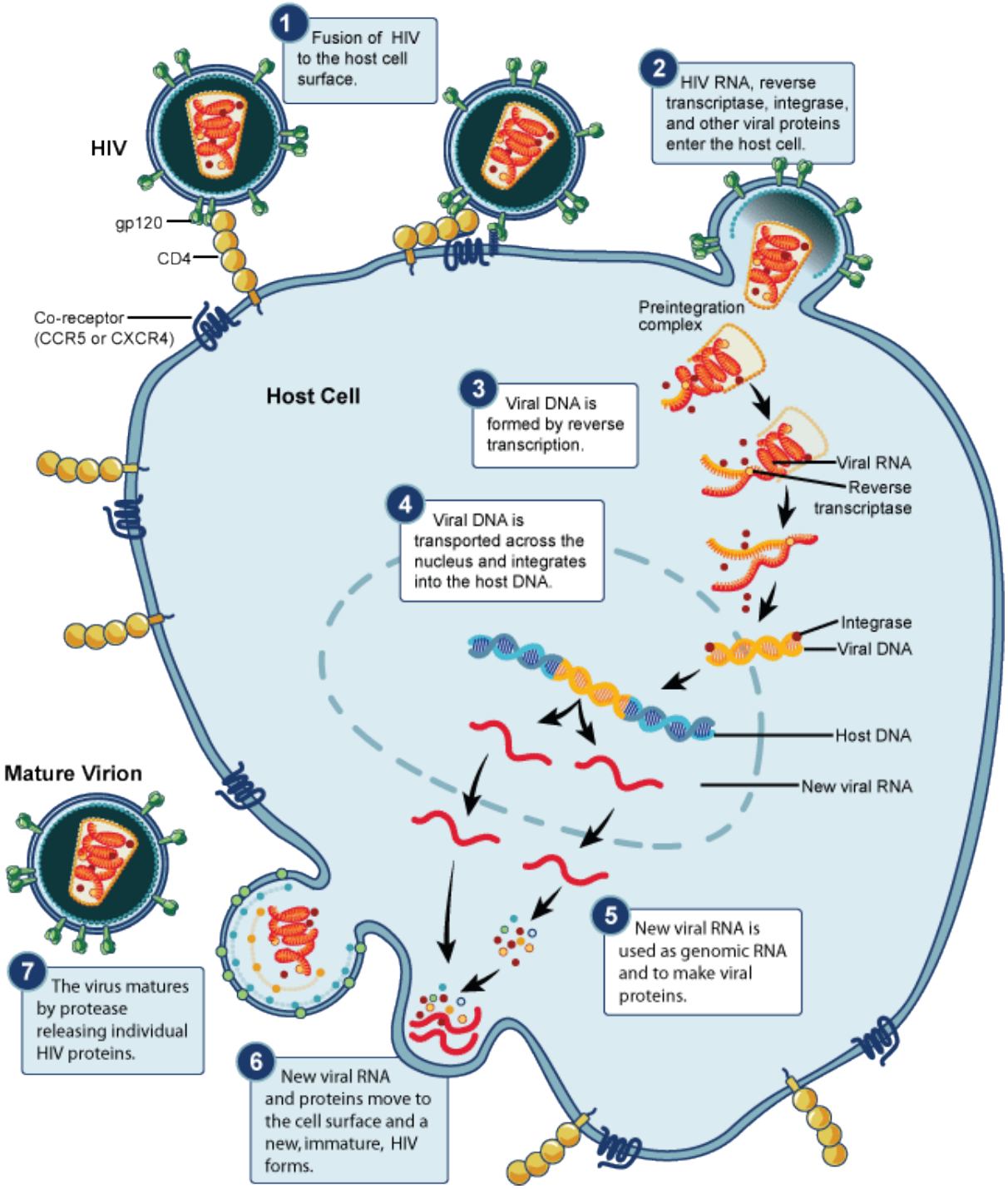


HIV-1 - Structure including components

The reverse transcriptase enzyme also called as RNA-dependent DNA polymerase, is found within the virion core. This enzymereplicates the single-stranded RNA of the virus to a double-stranded DNA intermediate. This viral DNA serves as the initiating precursor molecule needed for proviral integration, This takes place within the host cell genome. The core proteins of HIV-1 namely the capsid protein p24 and the matrix protein p18forms the major structure.

A bilayered lipid covering which is a part of the host cell outer limiting membrane surrounds the viral core protein structures. During replication, it is from this membrane that the virus buds from the cell surface. The envelope glycoproteins gp120 and gp41 cover this outer membrane. These glycoproteins are encoded by virus-specific genes. The outer envelope proteins are responsible for cell adhesion and entry.

Figure 3: LIFE CYCLE OF HIV



LIFE CYCLE OF HIV:

The virus by means of its surface protein gp120 begins its replication cycle by binding to the CD4+ T lymphocyte. It undergoes conformational change after entering the cell with the help of gp120. Then it attaches with one of the major HIV co-receptors CCR5 and CXCR4. The binding of HIV to CD4+ T cell, by binding the gp120 to C type lectin receptor on their surface by the dendritic cells is known as DC – SIGN. The penetration of the host cell membrane by the virion occurs with the help of the transmembrane protein gp41. The pre- intergration complex which comprises of the viral RNA and viral enzymes is released into the host cytoplasm surrounded by a capsid protein coat [31].

The target of the preintegration complex is the host cell nucleus. The RNA to DNA transcription is catalysed by viral **reverse transcriptase enzyme.** The resultant pro viral DNA is released from the nuclear capsid to enter the host nucleus. The enzyme **integrase** fuses the pro viral DNA with the host chromosome. The further course is variable. Either the provirus may now remain dormant or undergo different levels of genetic expression leading to production of large number of virions in the host.

The host cell on activation initiates transcription of the integrated pro viral DNA into RNA or mRNA.

The mRNA is modified by :

- Cleavage

- Glycosylation
- Phosphorylation
- Myristoylation

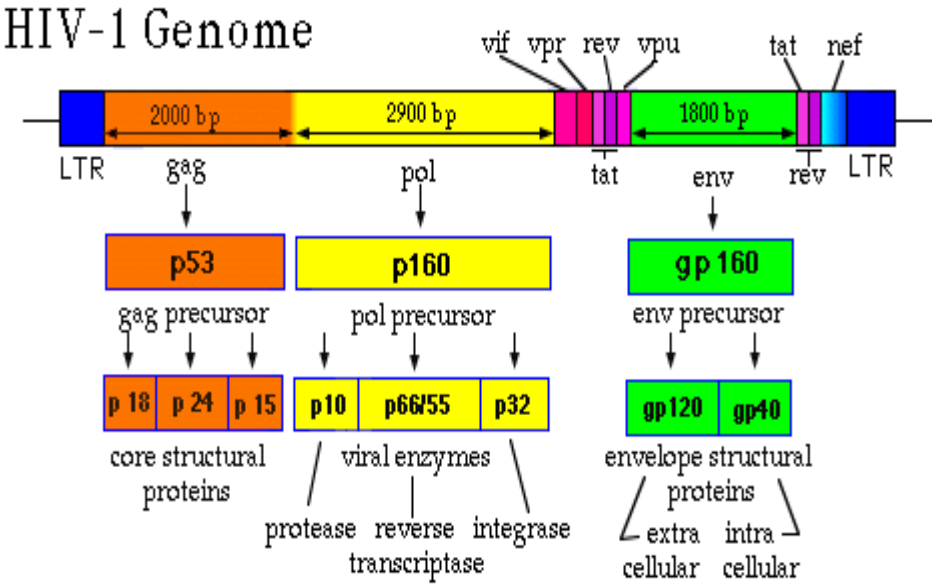
The assembly of the viral RNA, enzymes and proteins forms the entire virus particle. Lipid rafts are specialised areas of the host cell lipid membrane through which the virus buds out. The precursor proteins are cleaved by the viral enzyme **protease** to release the mature virion.

Each step is regulated by viral regulatory gene products which can be targeted for therapeutic interventions.

These include[24] :

- Virus – target cell binding
- Virus – target cell fusion
- Reverse transcriptase
- Integrase
- Protease.

Figure 4:MOLECULAR STRUCTURE OF HIV-1



GENOME AND ITS DIVERSITY:

There are numerous genes that code for functional and structural proteins.

GENE	FUNCTION
Env	Envelope glycoproteins
pol	Protease, reverse transcriptase and integrase enzymes
tat, rev, nef, vif, vpr, vpu	Regulates viral gene replication and host cell modification to enhance viral growth
gag	Core of virion (including p24 antigen)

The HIV 2 genome has vpx gene and lacks vpu gene which is present in HIV 1. The cluster mutations occurring in the surface proteins accounts for the genomic diversity of HIV. The genomic reverse transcriptase is more or less conserved. These diversities lead to subclassifications into groups, subtypes and sub – subtypes .

GROUPS[24]:

- 4 groups – group N, group M (major), group P and group O (outlier),
- Group M is subclassified into 9 different subtypes : A, B, C, D, F, G, H, J and K.

- Patients may be infected with more than one subtype which give rise to CRFs in combination (circulating recombinant forms). Examples include CRF02_AG and CRF01_AE
- Subtype A and F are then sub classified into sub – sub – types like A1, A2 and F1, F2.
- The geographic distribution of these different strains is widely distributed. Subtype C is the most prevalent strain all over the world.
- Other common strains globally are CRF01_AE, CRF01_AG, A, B, C, D, and G.
- There are numerous implications to this genetic diversity such as :

1. Different rates of disease progression
2. Varied response to therapy
3. Development of resistance
4. Continuous viral evolution
5. Inability to produce vaccine against wide range of strains

GEOGRAPHIC DISTRIBUTION OF VARIOUS HIV STRAINS:

1.	India	Subtype C
2.	China	Subtypes B, C and BC recombinant forms
3.	Western Europe	Subtype B
3.	Eastern Europe	Subtype A,B and AB recombinant forms
4.	Sub-Saharan Africa	Subtype C (most common) Subtype B and G, CRFO2_AG
5.	Australia	Subtype B
6.	Southeast Asia	CRF01_AE
7.	North America and some parts of South America	Subtype B

NEW EMERGING STRAINS:

CRF35_AD	Afghanistan and Iran*
BF recombinant forms	South America
CRF14_BG	Spain* Portugal*
Thai B. Indian C.	southern China*
CRF03_AB	Former soviet union

*predominantly among injection drug users

MODES OF TRANSMISSION:

Multiple ways of HIV transmission are:

- Sexual contact
- Vertical
- Perinatal
- Breast milk.
- Blood and blood products

No transmission has been reported through casual contact or insect bite.

SEXUAL TRANSMISSION[26,34]:

- May be homosexual or hetero sexual transmission
- Higher rates of transmission with higher HIV RNA load
- Increased risk with unprotected anal intercourse (receptive)
- Increased risk with genital infections (as increased number of inflammatory cells are present)
- Higher rate of transmission from male to female than vice versa
- Increased risk with genital ulcers caused by Chlamydia, Trichomonas, Neisseria, Herpes etc. due to exposed mucous membrane
- Due to absence of fore skin, male circumcision decreases risk of male transmission (decreased local concentration of inflammatory cells, decreased susceptibility to ulcerative infections, micro trauma)
- Due to immature genital tract, adolescent girls are more susceptible to infection.

TRANSMISSION BY BODY FLUIDS[26,27]:

- Screening of blood and blood products for presence of HIV antibodies, HIV p24 antigen and HIV RNA is practiced in most countries
- Transfusion related transmission cannot be completely avoided as HIV RNA levels cannot be detected in the first 10 – 15 days following infection due to undetectable levels of viremia, despite best technology
- HIV transmission can occur through transfusions of whole blood, plasma, factor concentrates in haemophiliacs, leukocytes and platelet concentrates
- No transmission occurs via hepatitis B Immunoglobulin, Rh immunoglobulin, hyper immune gamma globulin and plasma derived hepatitis B vaccine.

TRANSMISSION IN INTRAVENOUS DRUG USERS:

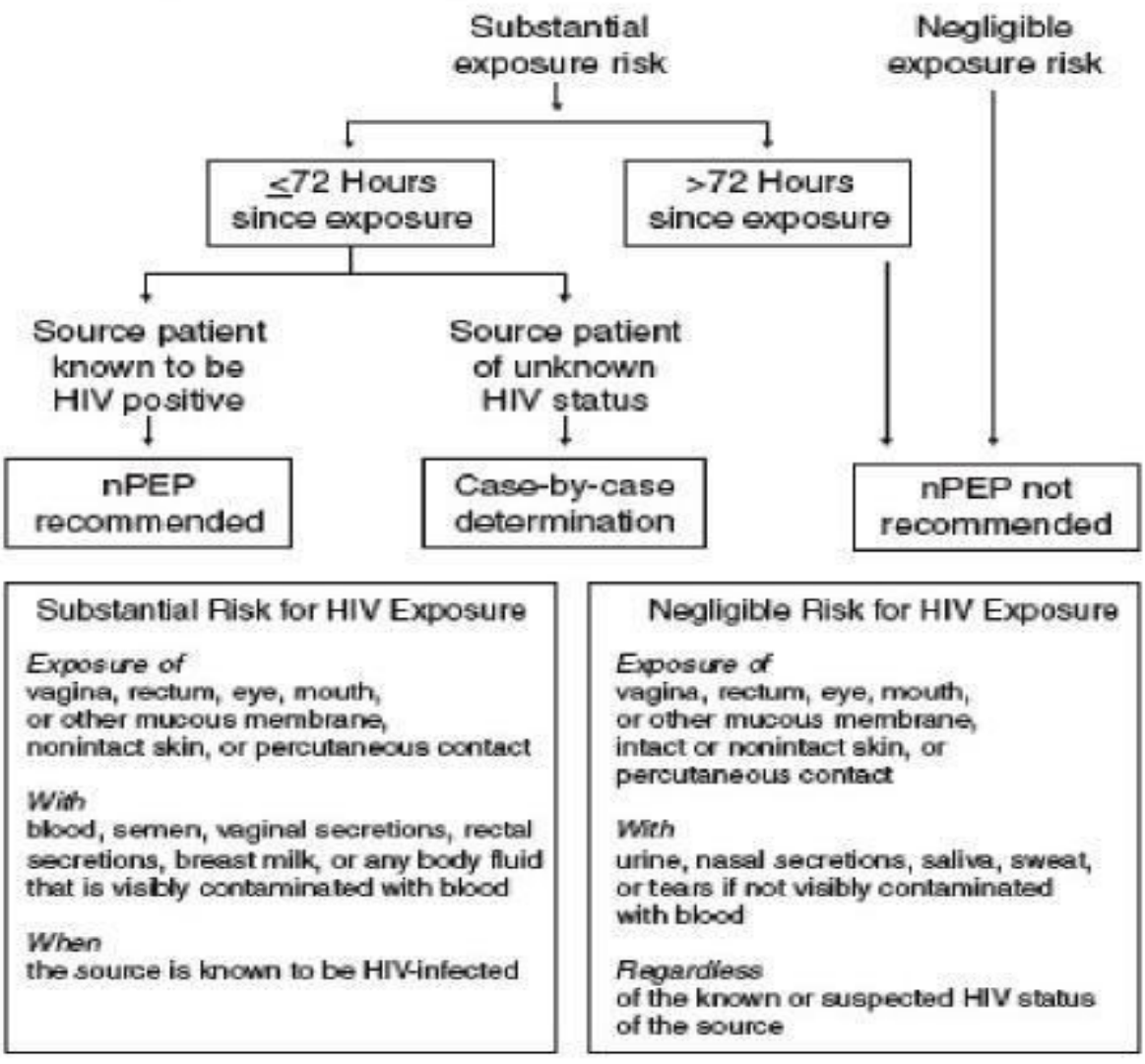
- Transmitted in injection drug abusers by sharing needles and drugs[27].
- Their sexual partners are also affected through homosexual or heterosexual transmission.
- Their children are affected through perinatal transmission of HIV infection.

TRANSMISSION IN HEALTH CARE WORKERS[26,27,28]:

Health care workers and laboratory personnels are at risk of procuring HIV infection from patients

- Risk due to contact of infected blood with mucous membrane or breached skin by needle stick injuries or cuts
- Increase risk of transmission by contact of blood with intact skin has not been documented
- Other potentially infectious body fluids are:
    - Pleural
    - Peritoneal
    - Cerebrospinal
    - Pericardial
    - Semen
    - Vaginal secretions
    - Synovial
    - Amniotic fluids
- No substantial risk of transmission: Saliva, sputum, sweat, feces, nasal secretions, vomitus, urine and tears.
- Transmission increases with long contact, large volume blood contact and port of entry in debraded mucous membrane or breached skin.
- Post exposure prophylaxis is warranted within 24 hours, in case of accidental exposure.
- Universal precautions with specialized disposable kits should be used while handling infected individuals.

Figure 5: POST EXPOSURE PROPHYLAXIS



UNIVERSAL PRECAUTIONS:

- Safe hand washing with soap and water
- Disposable gloves
- Protective long gowns
- Protective eyewear/ goggles
- Mask
- Heat inactivation or chemical decontamination of reusable equipments
- Blood spills- disinfection/ disposal
- Impervious containers- sharps disposal
- Caution of workers with raw area, denuded skin, active dermatitis etc.

FETO – MATERNAL TRANSMISSION[34]:

- Maternal Transmission to fetus can occur antenatally, during labour or during breast feeding.
- Higher risk of transmission are associated with :
  - ✓ Low maternal CD4 count
  - ✓ Pre term delivery
  - ✓ High maternal plasma viremia
  - ✓ Long duration between rupture of amniotic membrane & delivery
  - ✓ Procedures like amniocentesis, amnioscopy, episiotomy etc.
  - ✓ Close match of maternal and fetal human leucocyte antigen
  - ✓ Chorioamnionitis/STD during pregnancy
  - ✓ Hard drug use/ cigarette smoking during pregnancy.

TRANSMISSION BY BREAST FEEDING:

Transmission by breast milk is high during the early months of breast feeding

- Risk is increased with :
    - ✓ Mastitis
    - ✓ Low maternal CD4 count
    - ✓ Detectable levels of HIV in breast milk
    - ✓ Maternal vitamin A deficiency
- Risk of maternal transmission can be reduced by providing Zidovudine with or without lamivudine, to the mother in the last few weeks of gestation and to the fetus during the first week postnatally.
- Perinatal transmission risk is reduced by :
    - ✓ Anti retro viral prophylaxis antenatally
    - ✓ Reducing exposure of fetus to maternal blood and genital secretions (LSCS)
    - ✓ Universal voluntary testing / counselling of all pregnant women
    - ✓ Avoiding breast feed in high risk cases

PATHOGENESIS OF HIV:

HIV disease is a chronic infection which eventually leads to a quantitative and qualitative immunodeficiency because of ongoing immune destruction. Mechanisms by which this immune dysfunction is achieved are:

- Destruction of the immune cells by the replicating virus
- Indirect effects like clearance of infected immune cells by the reticulo endothelial system
- Excess immune activation leading to immune exhaustion
- Activation induced apoptosis (cell death).

The virus gains entry into the body by dendritic cells on the surface of mucosa or through microscopic rents in the mucosa. The virus then seeks its target -CD4+ T lymphocyte. The lymphocyte may be resting or activated. The activated T cells help in virus replication. It then spreads to the nearby draining lymph node where CD4 lymphocytes are available in large amounts. This causes an initial burst of viremia and wide dissemination of virus in primary infection leading to an early acute HIV syndrome[24].

Despite the massive immune response generated against acute viral infection, the virus is never eliminated from the human system and progresses to a chronic infection. The replication and immune destruction continues for almost 10years before the patient begins to deteriorate clinically.

\

PROTEINS THAT PLAY A VITAL ROLE IN PATHOGENESIS:

CD4	Surface protein on T lymphocytes
Gp 41	Transmembrane protein helps to penetrate host membrane and coil upon itself thereby helping in fusion
Gp120	CD4 receptor ligand, numerous spikes over the envelope of the virion
CCR5	beta chemokine receptor for host cells like lymphocytes, dendritic cells, macrophages and glial cells
CXCR4	Co receptor used by HIV during late stages of infection

FUSION:

Gp120 of the virus gets attached to CD4 molecule which is found in T helper cells. Gp120 undergoes conformational change. This leads to exposure of another underlying protein Gp41 present beneath Gp120. It also causes binding to host cell through co-receptors CCR4/CXCR5. Gp41 penetrates the host membrane, succeeds in bringing together viral and cellular membrane resulting in fusion.

FOUNDER VIRUS:

All viruses of infected individual do not transmit disease. The virus during its replication in various lymphoid tissues acquires extreme genetic expression and diversity. So there is a high degree of variation in genetic characteristics and immunological response of existing virus in the plasma and the initial founder virus [17]

CHARACTERISTICS OF FOUNDER VIRUS:

1. Minimal N-linked Glycosylation
2. Limited genetic diversity
3. Rapid divergence after transmission
4. Presence of effective neutralizing antibodies in TP*
5. Under representation in the plasma viremia of TP*
6. Short V1-V2 loop

*TP-Transmitting partner

IMMUNE SYSTEM EVASION OF HIV[24]:

The Human Immunodeficiency virus dodges all the defence mechanisms mounted against it and makes way for ambient survival conditions inside the host. Thus HIV infection is almost impossible to eradicate from the infected individual.

The mechanism by which the virus evades the immune system includes:

- Wide diversity of mutations and recombinations causing a sustained level of chronic viremia.
- The Nef protein on the virus downregulates the HLA class I antigens on the virus affected cells and hence escapes immune recognition.
- Mutant virus population that helps virus propagation by escaping recognition and destruction of the virus by CD8+ cytolytic cells.

- The neutralising antibodies are directed only against gp120 and gp41 of HIV because of:
    - ✓ Hypervariable regions in the genetic sequence of the envelope proteins.
    - ✓ post translational modification like glycosylation.
    - ✓ Conformational masking of antigenic epitopes.
- Sequestration of the infected cells preferentially in the immune previledged sites like central nervous system to avoid detection.
- Infection of virus specific CD4 cells selectively leading to elimination of virus specific immune response, with a profound damage to immune regulation and control of infection.

VIRAL RESERVOIRS AND LATENCY:

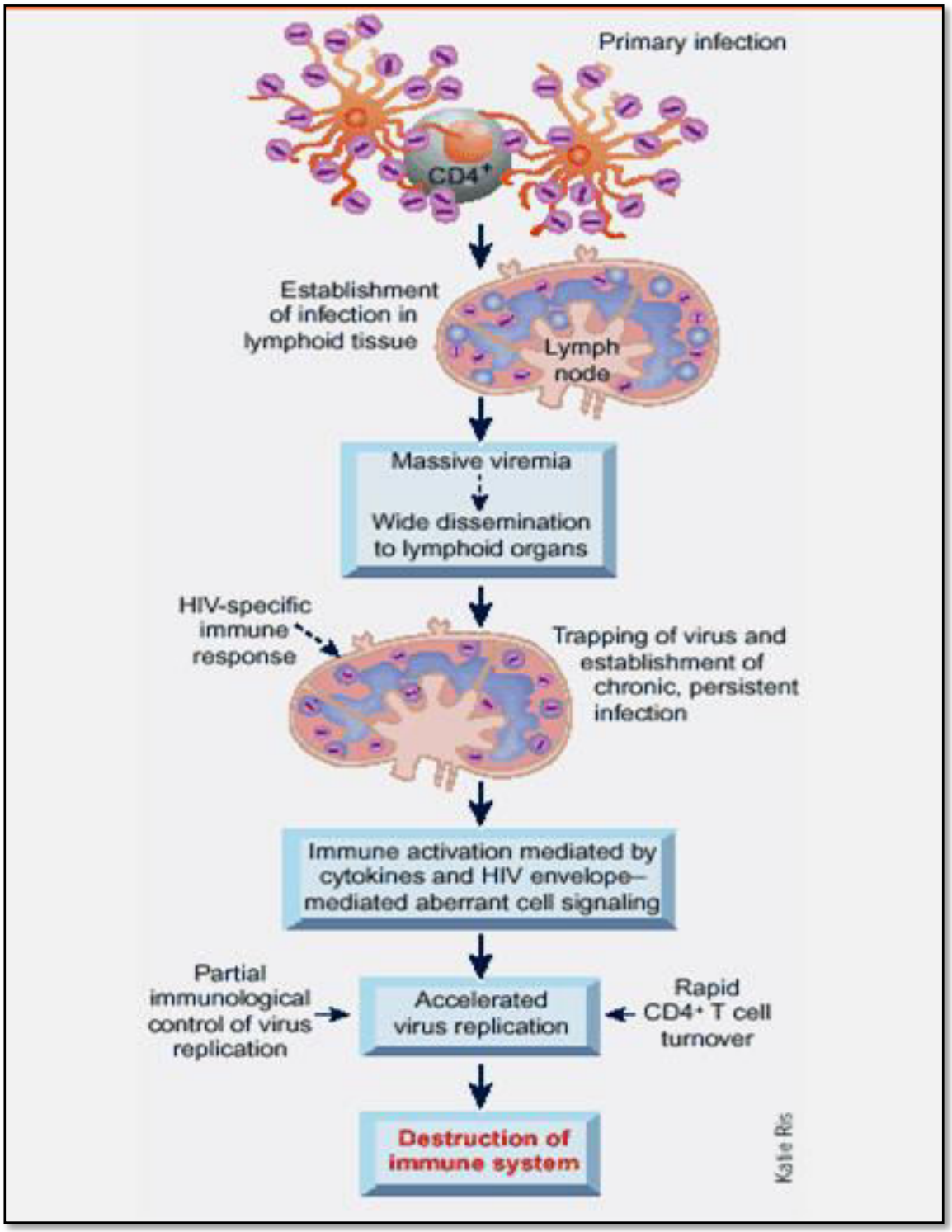
The wide range of infected cells in the dormant state in the body which act as a potential virus reservoir, is the greatest obstacle to eradication of HIV. These viral reservoirs exhibit pre – integration or post – intergration latency[24].

Pre – intergration latency is caused when the virus enters an inactive CD4 cell, and the reverse transcription is incomplete and the pro viral DNA is unable to immediately intergrate into the host genome . This phase can last for hours to days. The pro viral DNA degenerates, if no host cell activation occurs within this period.

Post – intergration latency is caused when the virus enters into an active host CD4 cell and the pro viral DNA integrates into the host cell genome following which the host cell remains dormant but can replicate upon receiving an activation signal from cytokines.

Reservoirs of HIV genome –exist in peripheral blood, lymph nodes, central nervous system and in other unidentified areas either active or in dormant form. Once the infection is established there is a progressive rise in the viral load and a progressive gradual decline in the CD4 cell count. This asymptomatic period is called clinical latency. It does not include microbial latency as there is continuous viral replication despite the absence of clinical features.

Figure 6:PATHOGENESIS



PATHOGENIC PROCESS IN LYMPHOID ORGANS:

The major site for virus proliferation is the lymphoid organs. Rather than the plasma viremia, it is the true index of disease activity. After the initial infection the virus enters the lamina propria of the mucosa in the scattered lymphoid cells. It then replicates in the gut associated lymphoid tissue GALT. After that the virus undergoes amplification, replication and dissemination.

Then the virus migrates to the draining lymph nodes where a greater concentration of lymphocytes is present which further promotes viral growth. This causes lymphadenopathy due cellular activation inside the lymph nodes which may be transient or generalised and persistent. Entry into the follicular dendritic cell is the next step which is found in the lymph node germinal center. These dendritic cells trap the intracellular and extracellular virions in its tender processes. These viruses persist in the lymph nodes for long duration and finally undergo a transition from acute to chronic persistent infection.

The follicular dendritic cells, which are antigen presenting cells, present the viral antigens to the B lymphocyte. This triggers the production of antibodies and cytokines, which bring more immune cells leading to persistent immune activation. This inflammation leading to germinal centre hypertrophy and aiding continuous viral replication setting up a vicious cycle of immune activation and viral multiplication.

Over time, the disease progresses to an advanced stage and the follicular dendritic cells are destroyed, with irreversible damage to the germinal centre due to collagen deposition. This leads to immune cell exhaustion and lymph nodes are burnt out, leading to profound immune deficiency ultimately[35].

PATHOGENESIS DUE TO IMMUNE ACTIVATION:

Immune activation and inflammation are the normal responses to any invading foreign antigen by the immune system. But in HIV infection , the aberrant immune response itself aids in viral replication and chronic persistent infection. Viral replication is most productive in activated immune cells. There are many factors that can produce immune activation and thus enhance the process of immune destruction by HIV.

These are:

- Co – infection with Epstein – Barr virus, parasite infestation, herpes, cytomegalovirus, tuberculosis and malaria. They accelerate the course of HIV infection.
- HIV is associated with the process of enhanced apoptosis and it causes exacerbation of various autoimmune conditions like anti phospholipid antibody syndrome, idiopathic thrombocytopenic purpura, Graves disease, psoriasis etc.
- Certain medical conditions which lead to persistent immune activation[11]:
    - ✓ Diabetes
    - ✓ Cardiovascular diseases
    - ✓ Liver disease (cirrhosis, hepatitis)
    - ✓ Accelerated aging syndromes
    - ✓ Dementias and other neurocognitive dysfunctions
    - ✓ Chronic kidney disease (any etiology)
    - ✓ Malignancies
    - ✓ Osteoporosis and other bone diseases.

CD4 DEPLETION:

There is an enhanced lymphocyte turnover rate and destruction in HIV. The depletion of CD4 cells occur by various mechanisms[35]:

DIRECT MECHANISMS

- Gp120 self fusion with CD4 intracellularly
- Interference with RNA processing
- Formation of syncytia
- Viral budding causing loss plasma of membrane intergrity
- Accumulation of unintergrated pro viral DNA

INDIRECT MECHANISMS

- Enhanced apoptosis
- Elimination of infected cells by virus specific immune responses.
- Activation induced cell death
- Inability to kill viral antigen coated cells
- Decreased lymphocyte generation
- Abnormal signalling pathways intracellularly
- Autoimmunity.

IMMUNE RESPONSES :

The primary HIV infection calls for a massive immune response including both humoral and cell mediated immune systems :

HUMORAL	CELL MEDIATED
▪ Enhancing antibodies	▪ Inhibitory CD8+ T cells
▪ Complement activation	▪ Natural killer cells
▪ Neutralising antibodies	▪ Cytolytic CD8+ T cells
▪ Antibodies in antibody dependant cellular cytotoxicity	▪ Antibodies in antibody dependant cellular cytotoxicity
▪ Binding antibody	▪ Inhibitory CD4+ T cells

PROTEINS WITH ANTIVIRAL ACTIVITIES IN HUMAN CELLS:

1. APOBEC3G
2. TRIM5α
3. TETHERIN

APOBEC3G:

It acts on viral genome and substitute adenosine in the place of guanine in the viral genome. It causes suppression of viral transcription. The virus overcomes its action by ubiquitinisation and degradration of the protein. This is carried out by vif gene of the virion[19].

TRIM5α:

This protein causes premature uncoating of viral nucleocapsid in cellular cytoplasm. This cellular antiviral mechanism is evaded by producing variation in capsid protein.

TETHERIN:

This is a newly discovered molecule present in the host cytoplasm called CD317. It inhibits budding of the formed virus through cellular membrane. Viruses are sequestered in tetherin mediated vesicles. Action of tetherin is inhibited by production of vpu protein by the virus.

DIAGNOSIS OF HIV:

The initial diagnostic test of HIV is the antibody testing using Enzyme Immuno Assay. EIA is the screening test of choice due to its high sensitivity. The newer modalities provide a shorter window period of detecting the virus[11].

- Nucleic acid testing – 12 days
- p24 antigen testing – 16 days
- Antibody testing (EIA) – 22 days

Initial screening test for HIV is EIA. The test usually reads positive (highly reactive), indeterminate or negative (non – reactive). The test has high sensitivity index. Thus, when the test results are negative HIV may be ruled out.

Figure 7: ALGORITHM FOR DIAGNOSIS OF HIV

False positive
Antibodies to HLA antigens
Multiple transfusions
Recent influenza immunisation
Improper specimen handling (e.g. heating)
Unknown

False negative
Recent infection (window period)
Hypogammaglobulinaemia
Advanced HIV infection (rare)
HIV-2 (applies only to test kits specific for HIV-1)
Unusual HIV-1 serotype (e.g. group O)

False positive reactions occur especially in pregnancy, transfusions, post transplantations, recent vaccinations, acute viral infections etc.

If EIA is indeterminate, it should be repeated twice. If it is negative then HIV is ruled out. But if one test is positive, then a confirmatory test with western blot should be done. If it tests positive, then the patient is termed HIV positive. If the test is indeterminate even with western blot, repeat test should be done after 3 months.

Other confirmatory test can be done like p24 antigen assay, HIV RNA assay, DNA PCR etc. All these tests are highly sensitive and can therefore can cause false positive results. Till date gold standard test would be EIA screening followed by confirmation with western blot. The other tests are used only when the conventional tests fail to provide confirmatory results[24].

MONITORING DISEASE ACTIVITY:

The two parameters giving a reliable index of disease activity in monitoring patients with HIV infection are CD4+ T cell counts and HIV RNA level assay. These tests can performed at the disease onset and in regular periods thereafter.

The CDC guidelines recommend that ART is started when the CD4 count is <500/µL. Drugs can be changed if the patient does not improve CD4 counts by atleast 25% after starting therapy.

- Counts <200/µL - Pneumocystis jirovecii pneumonia prophylaxis started
- Counts <50/µL - prophylaxis for MAC infections should be started

HIV RNA levels indicate the level of viremia of the patient. It is be checked at the onset of the disease and at 3 – 4 months interval thereafter. Once anti retroviral therapy is started, RNA levels usually reduce to <50 copies/ml within 6 months. After this the levels rise again and reach a new steady state. Monitoring is done every 4 weeks until the new steady state is reached and every 3 months thereafter[24].

CLINICAL FEATURES:

HIV produces a clinical spectrum ranging from asymptomatic to advanced immunodeficiency called AIDS. Patient may either present with opportunistic infections or pathogenic manifestation of the virus per se[36].

ACUTE HIV SYNDROME:

It develops after three to six weeks of infection in approximately half of the infected individuals. The symptoms are mostly self limiting and last only for few weeks. Due to acute reduction in CD4 counts, even opportunistic infections have been reported [24.]

Only one in ten infected patients will progress to fulminant disease. Sometimes patients deteriorate even after recovering from acute illness. Clinical manifestation during acute infection include :

Systemic symptoms:

- ✓ Headache
- ✓ Myalgia
- ✓ Vomiting
- ✓ Fever
- ✓ Lymphadenopathy
- ✓ Nausea
- ✓ Retro orbital pain
- ✓ Arthralgia
- ✓ Diarrhea
- ✓ Pharyngitis
- ✓ Malaise
- ✓ Weight loss

Cutaneous manifestations:

- ✓ Erythematous maculopapular Rash
- ✓ Mucocutaneous ulcers

Neurological manifestations[36]:

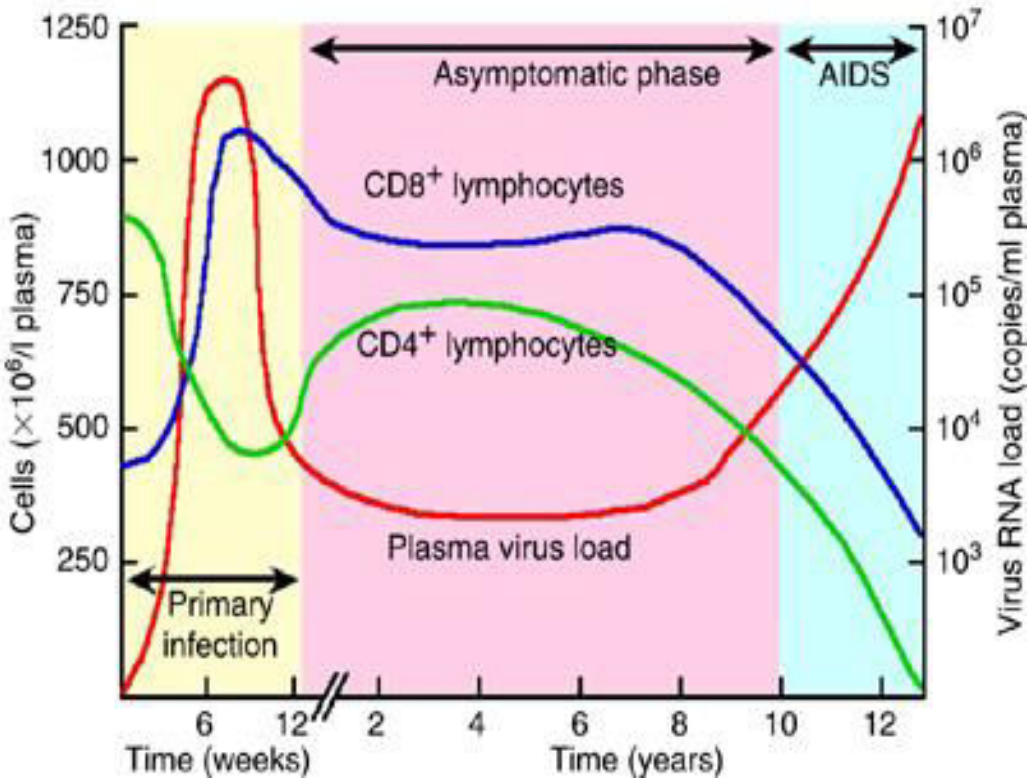
- ✓ Peripheral neuropathy
- ✓ Acute demyelinating Encephalomyelitis
- ✓ Headache
- ✓ Aseptic meningitis
- ✓ Acute transverse myelitis
- ✓ Encephalitis

ASYMPTOMATIC STAGE:

Symptoms of the patient disappear after the initial state of plasma viremia and acute HIV syndrome and there is recovery of immune function. There may be increase in the count of total CD8 cells[24].

But there is a steady decline in CD4 count. The count decreases by approximately 50 per year. Patient may be clinically silent even for a decade. But it is not microbiological or immunological latency. There is a continual destruction of immune system as well as progressive increase in viral load as the years advance even though patient is asymptomatic.

Figure 8: CLINICAL SPECTRUM WITH DECLINE IN CD4 COUNT



LONG TERM SURVIVORS:

Few patients remain asymptomatic even for a very long time. There are four such groups.

1. LONG TERM NON PROGRESSORS (LTNPs):

They are characterised by:

- Prolonged asymptomatic period that may last for more than two decades.
- Normal CD4 count.
- Very low plasma viral load
- Not on ARTs

2. ELITE CONTROLLERS:

These are special group of LTNPs. They are characterised by[24]

- Normal CD4 count.
- Strong immune response to virus
- Extremely low plasma viral load
- Over representation of HLA class I molecules.

3. PATIENTS ON ART :

The advent of the newer and effective HAART has revolutionized the treatment of AIDS on the face of the earth. When started early and monitored ART confers a healthier, longer and better quality of life to these patients[25].

4. ASYMPTOMATIC DECLINE:

Fourth group includes patients who are asymptomatic despite the declining immunity. CD4 continues to decrease. They suddenly manifests with opportunistic infections and detoriate[24].

THE ACQUIRED IMMUNODEFICIENCY SYNDROME:

Acquired immunodeficiency syndrome (AIDS) is defined in terms of either a $CD4^+$ T cell count below 200 cells per μL or the occurrence of specific diseases in association with an HIV infection. In the absence of specific treatment, around half of people infected with HIV develop AIDS within ten years. The most common initial conditions that make us to suspect the onset of AIDS are esophageal candidiasis, Pneumocystis carinii pneumonia (40%) and HIV wasting syndrome/ cachexia (20%). Opportunistic infections, virus induced cancers, neurologic and psychiatric manifestation are the other common signs.

Figure 9: CLINICAL PICTURE OF AIDS

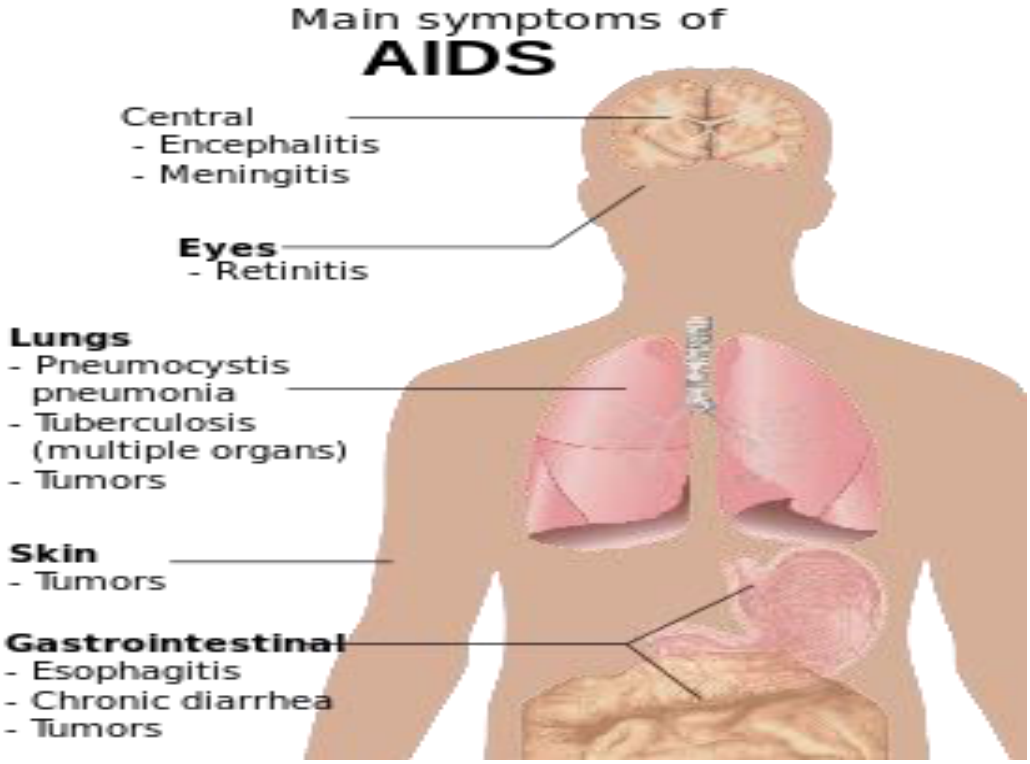
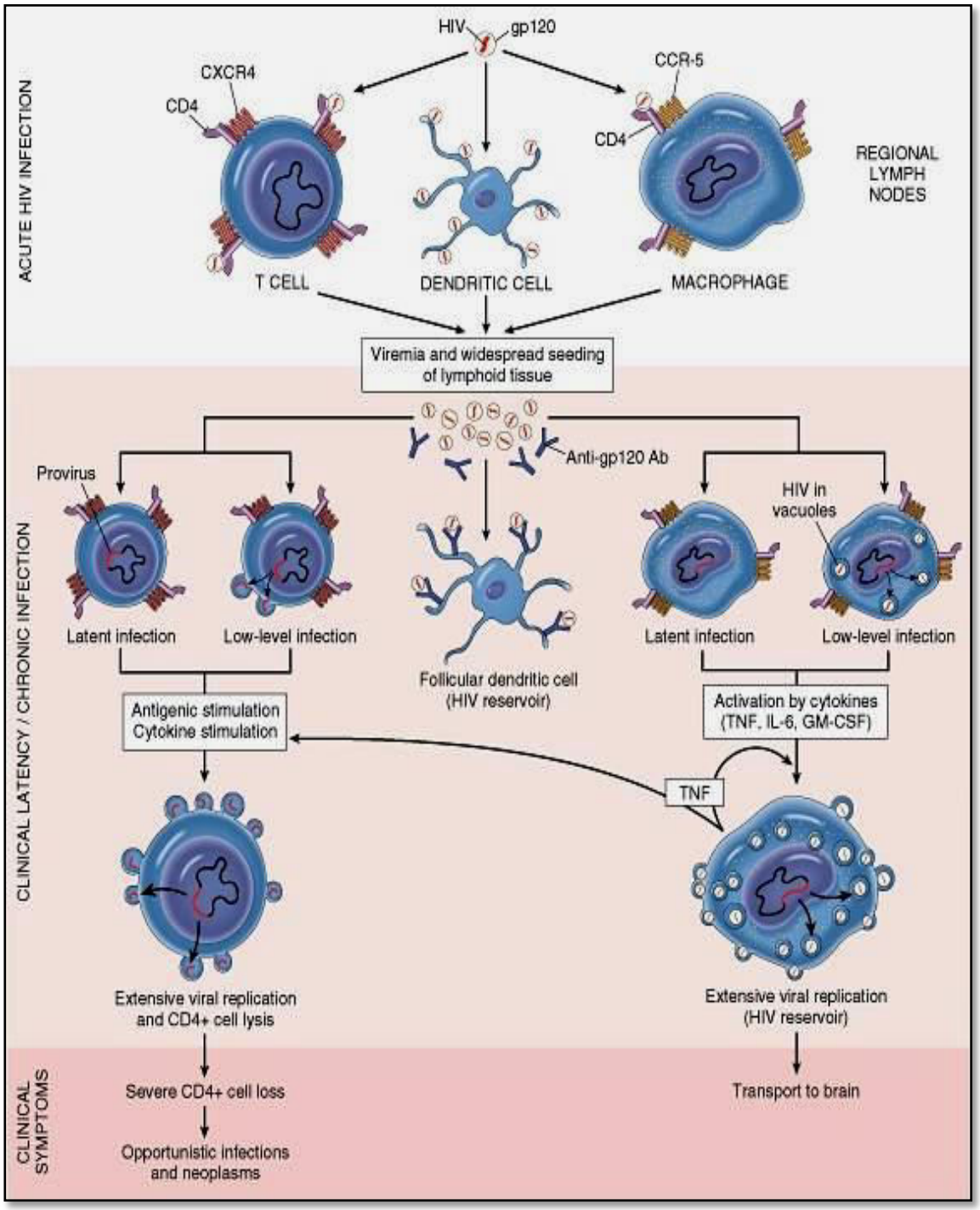
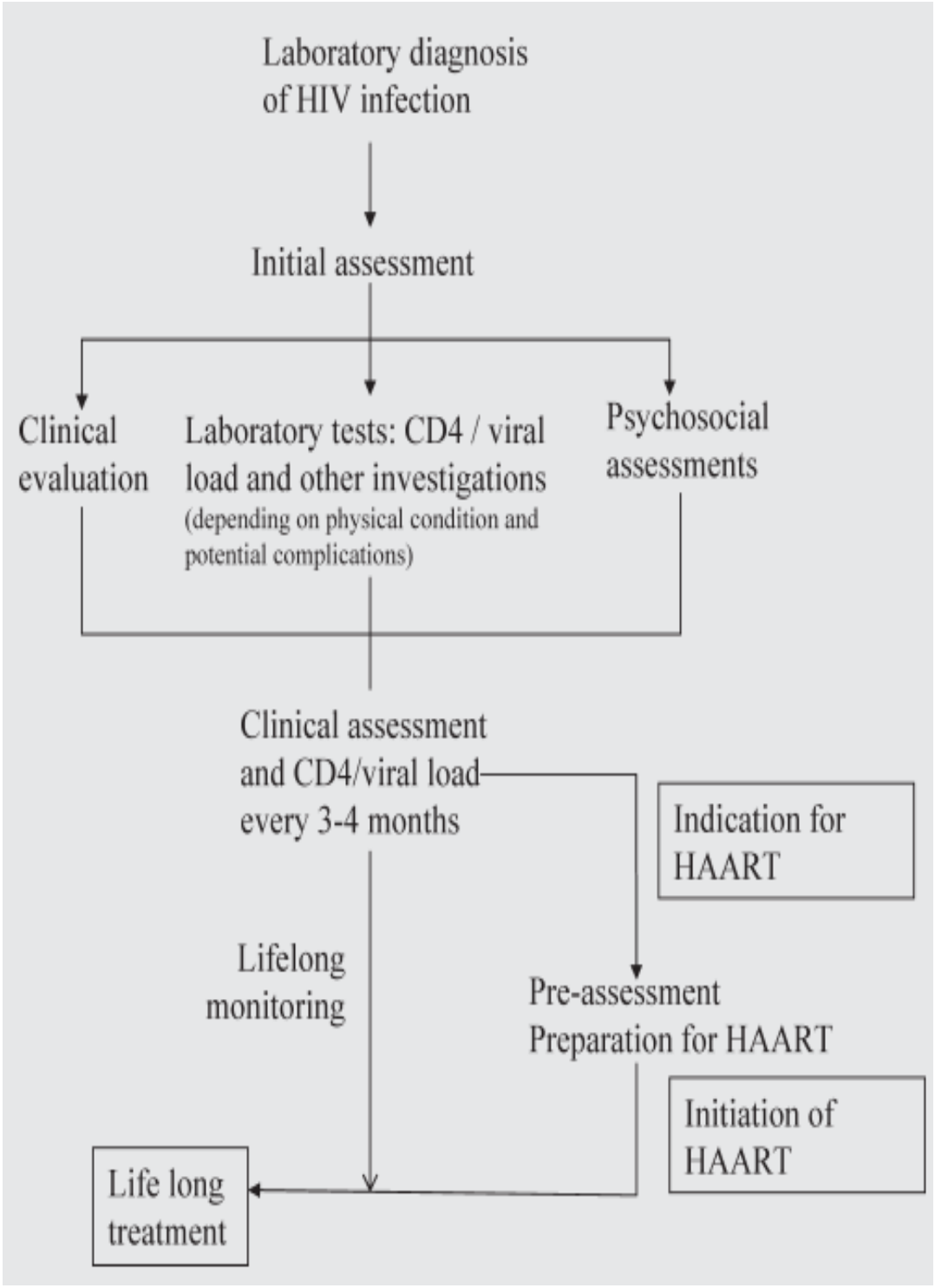


Figure 10: MECHANISM OF THE NATURAL HISTORY OF THE DISEASE



TREATMENT OF HIV:



HIGHLY ACTIVE ANTIRETROVIRAL THERAPY:

- Early initiation of Highly active antiretroviral therapy (HAART) is the recent concept in the management of patients with HIV infection.
- Overcomes resistant strains.
- Combination of two NRTIs plus one or two PIs or a NNRTI.
- Use of tenofovir and emtricitabine combined with efavirenz has the advantage of once daily dosing.
- Decreases the viral load and cause long term suppression of HIV RNA below levels of detection.
- Suppression of viremia and virus shedding in semen and vaginal secretions.

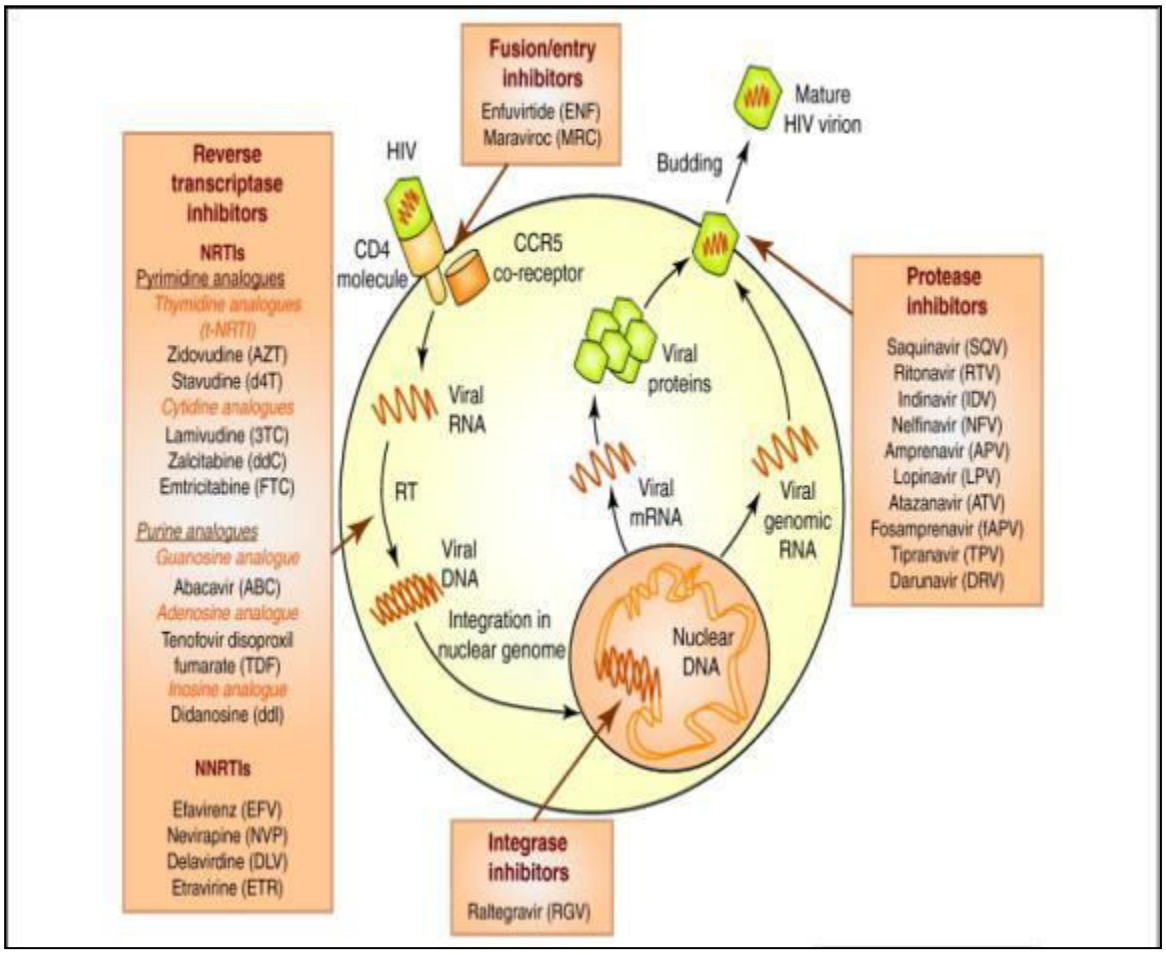
BENEFITS OF HAART:

- Fewer opportunistic infections and HIV-associated malignancies
- Increased CD4+ T cell count
- Prolonged survival
- Restoration of lymph node architecture
- Reduced immune activation
- Clinical improvement
- Ability to discontinue opportunistic infection prophylaxis and maintenance therapy.

SIDE EFFECTS OF HAART:

- Hyperlipidemia
- Lipoatrophy
- Abnormal fat accumulation
- Pancreatitis
- Insulin resistance
- Marrow suppression
- Neuropathy
- Hepatitis
- Bone loss
- Nephropathy

Figure 11: TARGETS FOR THERAPY



HIV ENDOCRINOPATHY AND METABOLIC DISORDERS:

Various mechanisms play a role in developing endocrine and metabolic abnormalities in HIV patients. Most common ones are:

- Secondary to opportunistic infections involving the gland
- Direct effect of HIV infection on the gland and metabolism
- Side effects of medication.

They are:

1. LIPODYSTROPHY:

- 30 – 75 % of patients receiving ART
- Increased total cholesterol, triglycerides, apolipoprotein B Hyperinsulinemia, hyperglycemia
- Truncal obesity with peripheral wasting
- 20% meet the criteria for metabolic syndrome
- Common in regimens with protease inhibitors, stavudine and zidovudine
- Treat with Gemfibrozil and Atorvastatin.

2. OSTEONECROSIS OR AVASCULAR NECROSIS OF BONE:

- On patients on ART, lipid lowering agents and steroids
- Common in hip and shoulders
- Diagnosed by MRI.

3. OSTEOPOROSIS:

- 7% of women with HIV
- 41% have osteopenia

4. LACTIC ACIDOSIS:

- Common with NRTIs and can be fatal

5. SIADH:

- Hyponatrenia
- Associated with pulmonary or CNS disease

6. ADRENAL INSUFFICIENCY:

- Hyponatremia and hyperkalemia.
- Due to mycobacterium infection, CMV, Cryptococcus, histoplasmosis or ketoconazole therapy.
- Hyperkalemia also due to HIV nephropathy, trimethoprim and pentamidine.

7. CUSHING'S SYNDROME:

- Patients using local steroids like inhalers while taking Ritonavir.
- Ritonavir inhibits CYP3A4 and prolongs the half life of steroids.

8. THYROID DYSFUNCTION:

- Both hypo and hyperthyroidism
- Most common is subclinical hypothyroidism
- 10% of patients on ART have increased TSH
- Opportunistic infections like pneumocystis jiroveci, CMV, toxoplasma may infect the gland causing non tender diffuse enlargement.

9. GRAVES DISEASE:

- Seen in immune reconstitution syndrome as a late complication.

10.HYPOGONADISM:

- 20-30% of men
- Due to chronic illness, Ganciclovir therapy
- Decreased libido, erectile dysfunction is also seen
- Treat with androgen replacement therapy

These endocrinopathies and metabolic disorders cause significant morbidity in HIV patients. It should be kept in mind and screened when they are suspected.

MATERIALS AND METHODS

STUDY POPULATION:

This study is to be conducted among 50 patients with Seropositive HIV, attending the Department of Medicine & ART Centre in Govt. Rajaji Hospital, Madurai.

INCLUSION CRITERIA:

- All HIV positive adult patients (Serology positive) attending ART Centre and also among in-patients of Department of Medicine, both sex.
- Age > 18 years.

EXCLUSION CRITERIA:

- Known cases of thyroid disorder.
- Patients on drugs altering thyroid hormone metabolism along with stavudine based anti-retroviral drugs.
- All Diabetics.
- Abnormal Liver function tests with SGOT/SGPT levels greater than 3 times normal range, and Renal function tests abnormalities with serum Creatinine more than 1.6mg%.

DATA COLLECTION:

- A Brief history with clinical examination will be done
- Detailed Clinical Examination
- HIV ELISA, CD4 Count
- T3,T4,TSH

LABORATORY INVESTIGATIONS:

- 1. T3,T4,TSH
- 2.CD4 Count

STUDY PROTOCOL:

In Patients of HIV Positive on ART, both sex, T3, T4, TSH, CD4 Count are done .Results are then analyzed.

DESIGN OF STUDY:

Prospective analytical study.

PERIOD OF STUDY:

JUNE 2014 TO SEPTEMBER 2014

COLLABORATING DEPARTMENTS:

- Department of Medicine
- Department of Endocrinology
- Regional ART Centre

ETHICAL CLEARANCE:

Approval obtained from the institutional ethical committee, Madurai Medical College and Government Rajaji Hospital, Madurai.

CONSENT:

Individual written and informed consent.

CONFLICT OF INTEREST:

NIL

FINANCIAL SUPPORT:

NIL

PARTICIPANTS:

Patients of Govt. Rajaji Hospital, Madurai who fulfil the inclusion criteria.

STATISTICAL ANALYSIS:

After obtaining the results, the data was compiled in a Microsoft Excel sheet. Statistical analysis was done using IBM SPSS Ver.20 (Statistical package for social sciences). Percentage prevalence, pvalues and standard deviation were calculated. The significance of relationship between groups was found out using Chi – Square test, logistic regression analysis and Student t test.

LIMITATIONS OF STUDY:

1.Small sample size.

2.Lack of availability of Thyroid Antibodies at baseline.

3.Role of single Antiretroviral drug has not been evaluated.

RESULTS AND ANALYSIS

Table 1: Age distribution of patients studied

Age in years	Number of patients	Percent
20-30	17	34
31-40	20	40
41-50	9	18
>51	4	8
Total	**50**	**100**

Comments : Mean ± SD: 36.50±10.25 ; Maximum - 54 years ;

Minimum - 20 years ;

Figure 12 : Percentage distribution of the patients studied

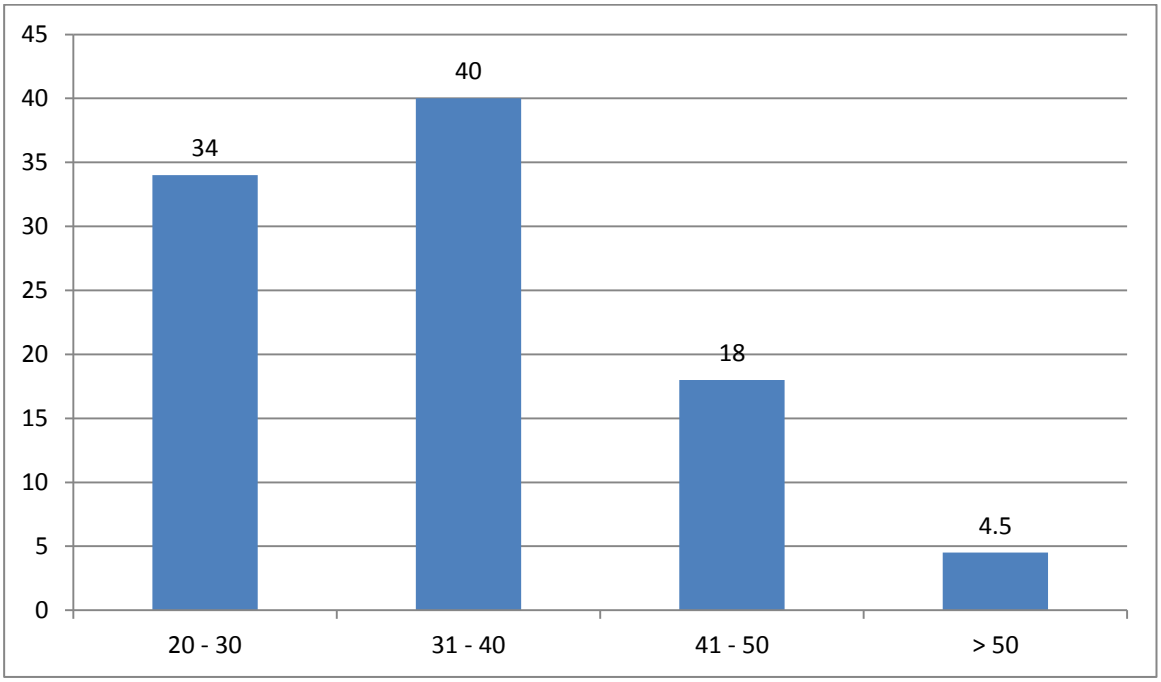


Table 2: Gender distribution of patients studied

Gender	Number of patients	Percent
Male	28	56.0
Female	22	44.0
Total	**50**	**100.0**

Comments: About 56 % were males and 44 % were females.

Figure13 : Gender distribution of patients studied

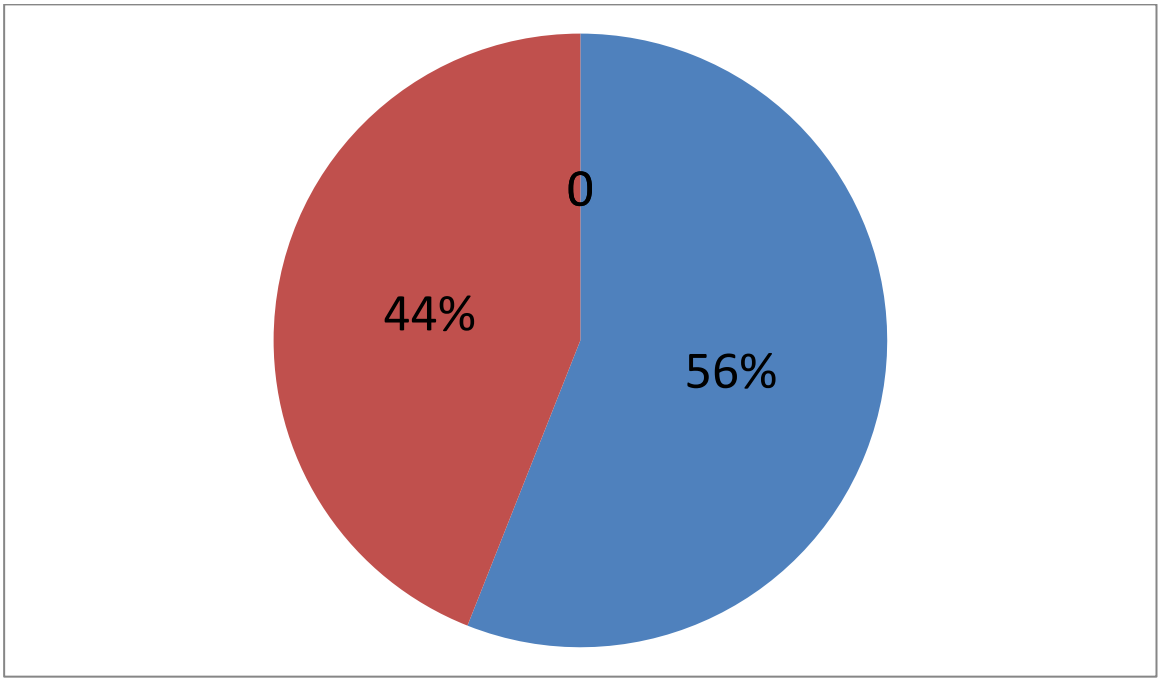


Table 3: CD4 count distribution of patients studied

CD4 count	Number of patients	Percent
<100	7	14.0
100-200	18	36.0
200-500	16	32.0
>500	9	18.0
Total	**50**	**100.0**

Comment : Mean ± SD: 311.46 ± 223.94

Figure14 : Percentage distribution of the CD4 studied in the population

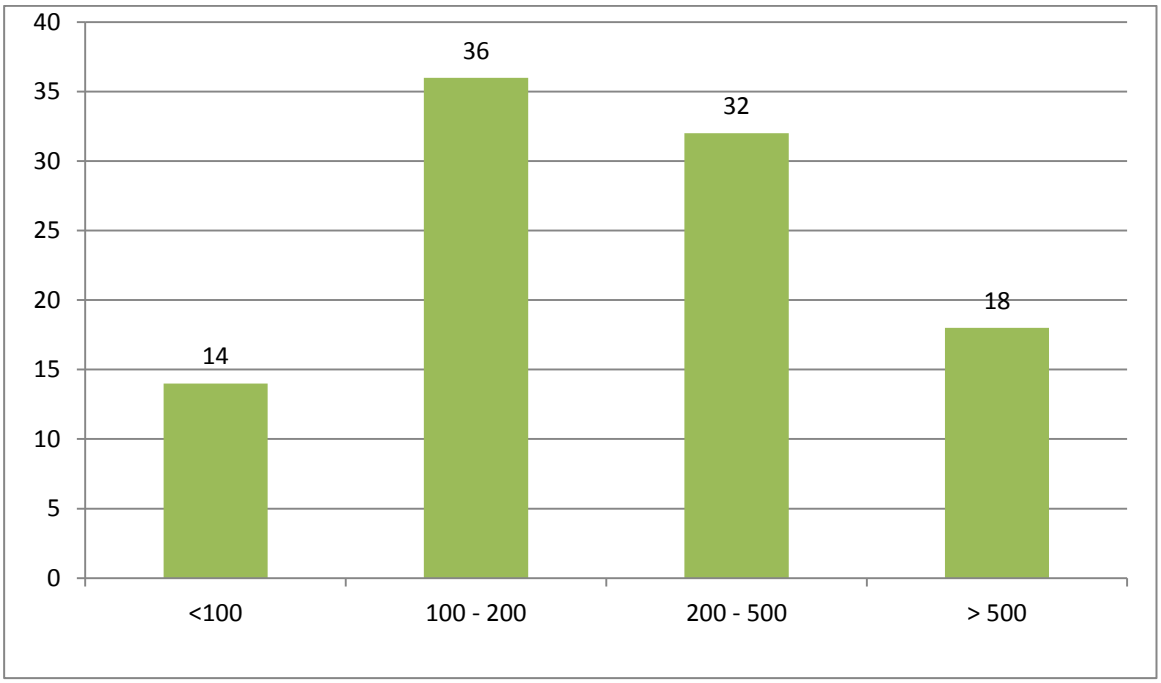


Table 4: Thyroid parameters of patients studied

Thyroid Parameters	No Of Patients (n=50)	%
T3		
<70	1	2.0
70-190	47	94.0
>190	2	4.0
T4		
<5.0	10	20.0
5.0-12.0	40	80.0
>12.0	0	0.0
TSH		
<0.5	0	0.0
0.5-5.0	21	42.0
>5.0	29	58.0

Figure15 : Percentage distribution of the thyroid profile studied

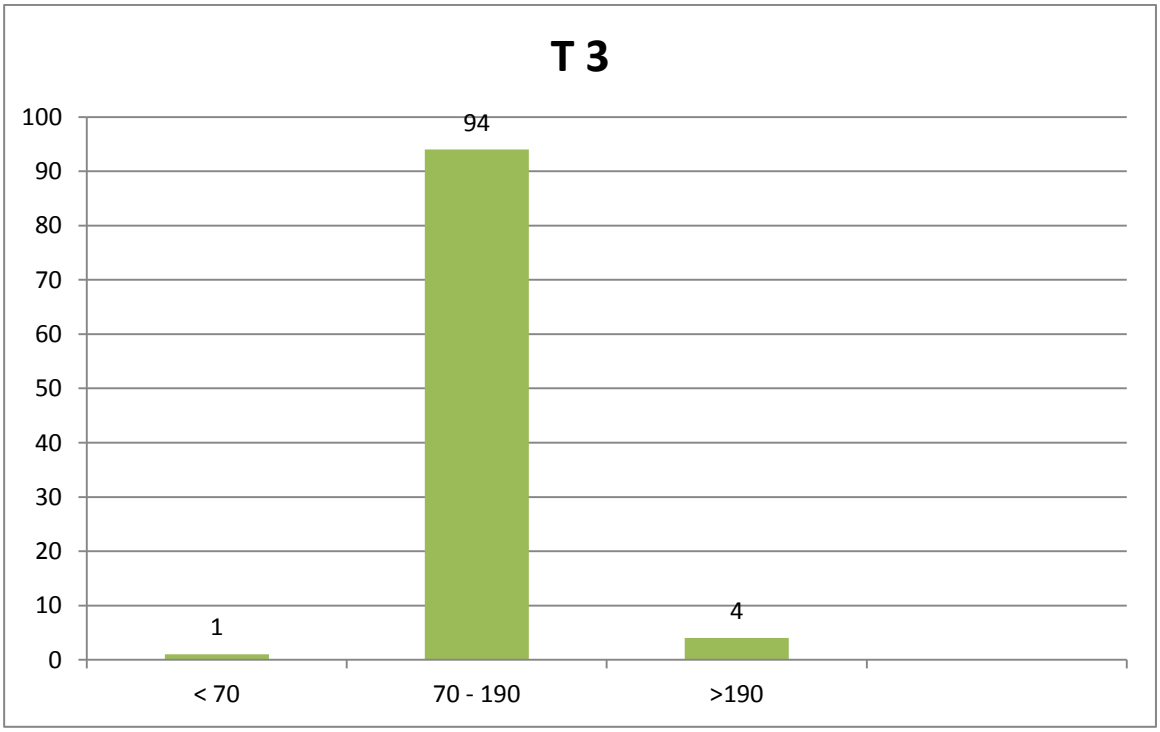


Figure16 : Percentage distribution of the thyroid profile studied

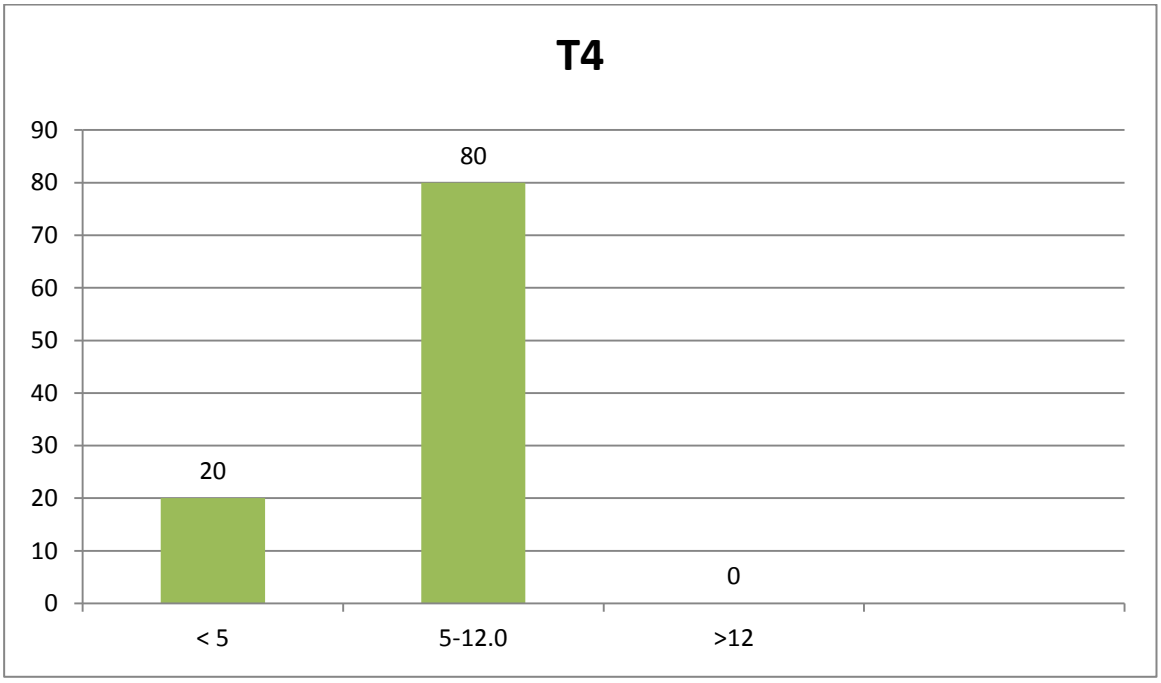


Figure17: Percentage distribution of the thyroid profile studied

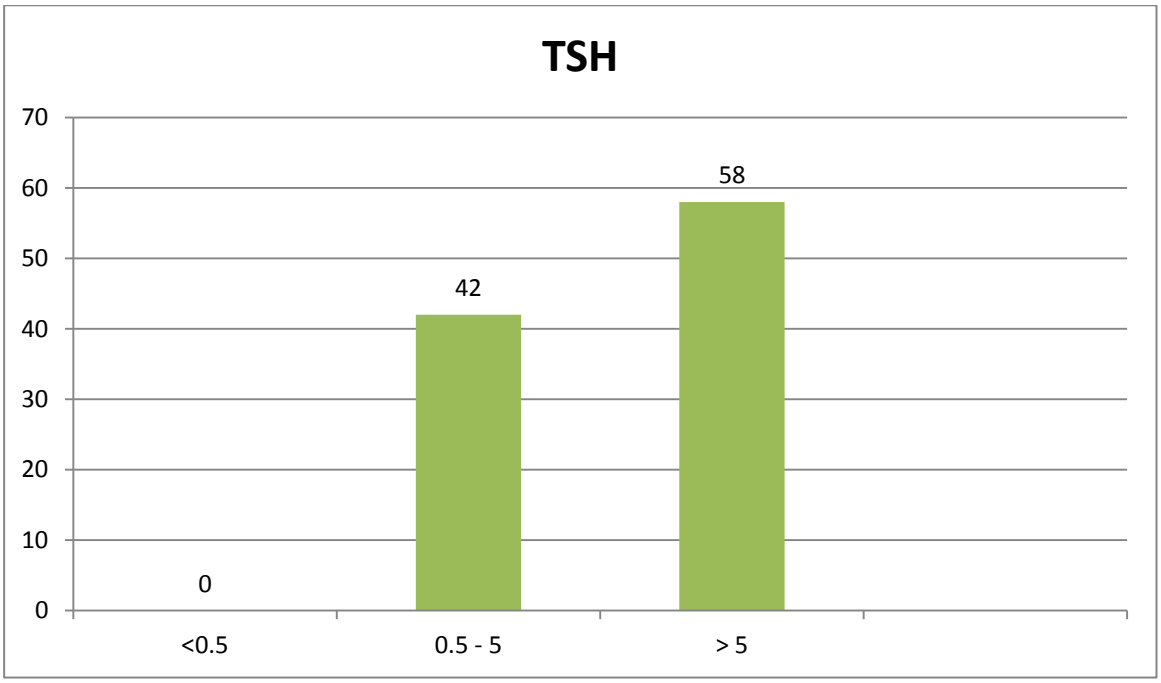


Table 5: Co relation of T3, T4 and TSH with CD4 count

Variables	CD4 Count					
	< 100 (n=7)	**100-200 (n=18)**	**201-500 (n=16)**	**> 500 (n=9)**	**Total (n=50)**	**P' Value**
T3	89.00+26.81	112.56+20.28	128.31+17.83	107.2+6.42	113.34+22.35	0.056 NS
T4	5.16+2.51	7.63+2.35	9.20+1.43	9.42+1.53	8.11+2.39	< 0.001**
TSH	9.75+0.39	8.14+0.32	3.99+0.95	3.48+0.69	6.34+1.06	< 0.001 **

Figure18: Co relation of T3 with CD4 count in the population studied in percentage

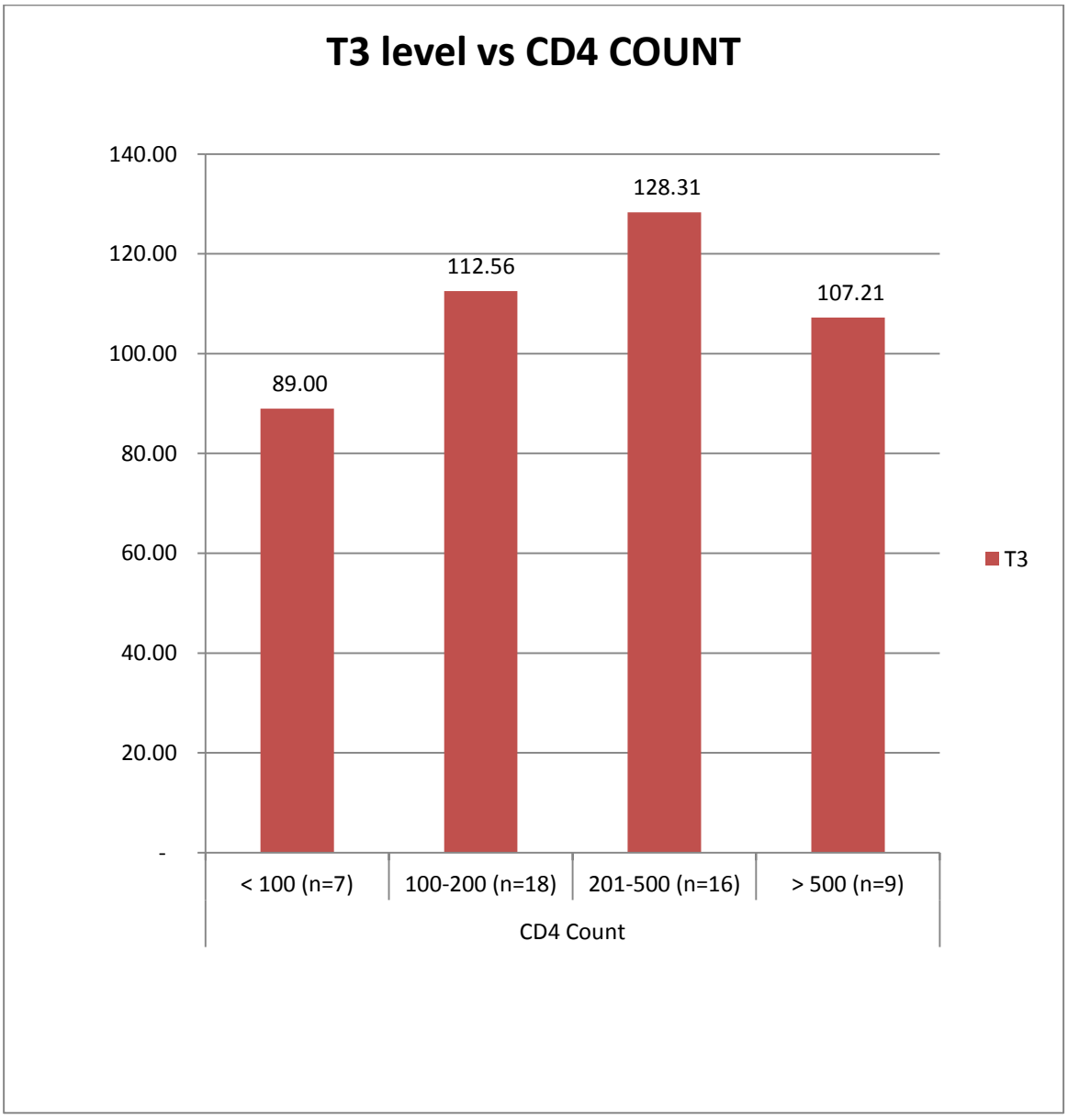


Figure19 : Co relation of T4 with CD4 count in the population studied in percentage

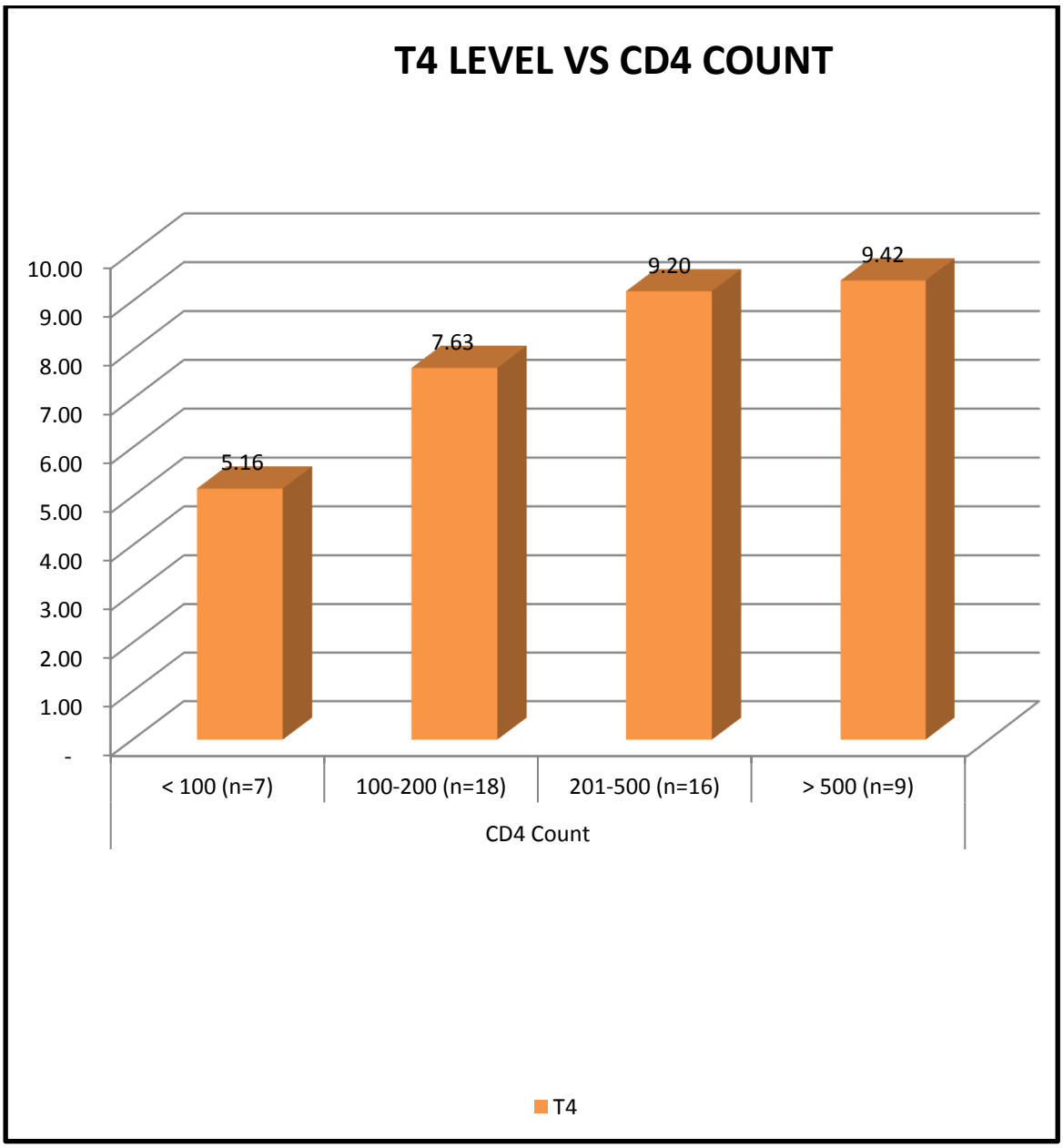


Figure20: Co relation of TSH with CD4 count in population studied (%)

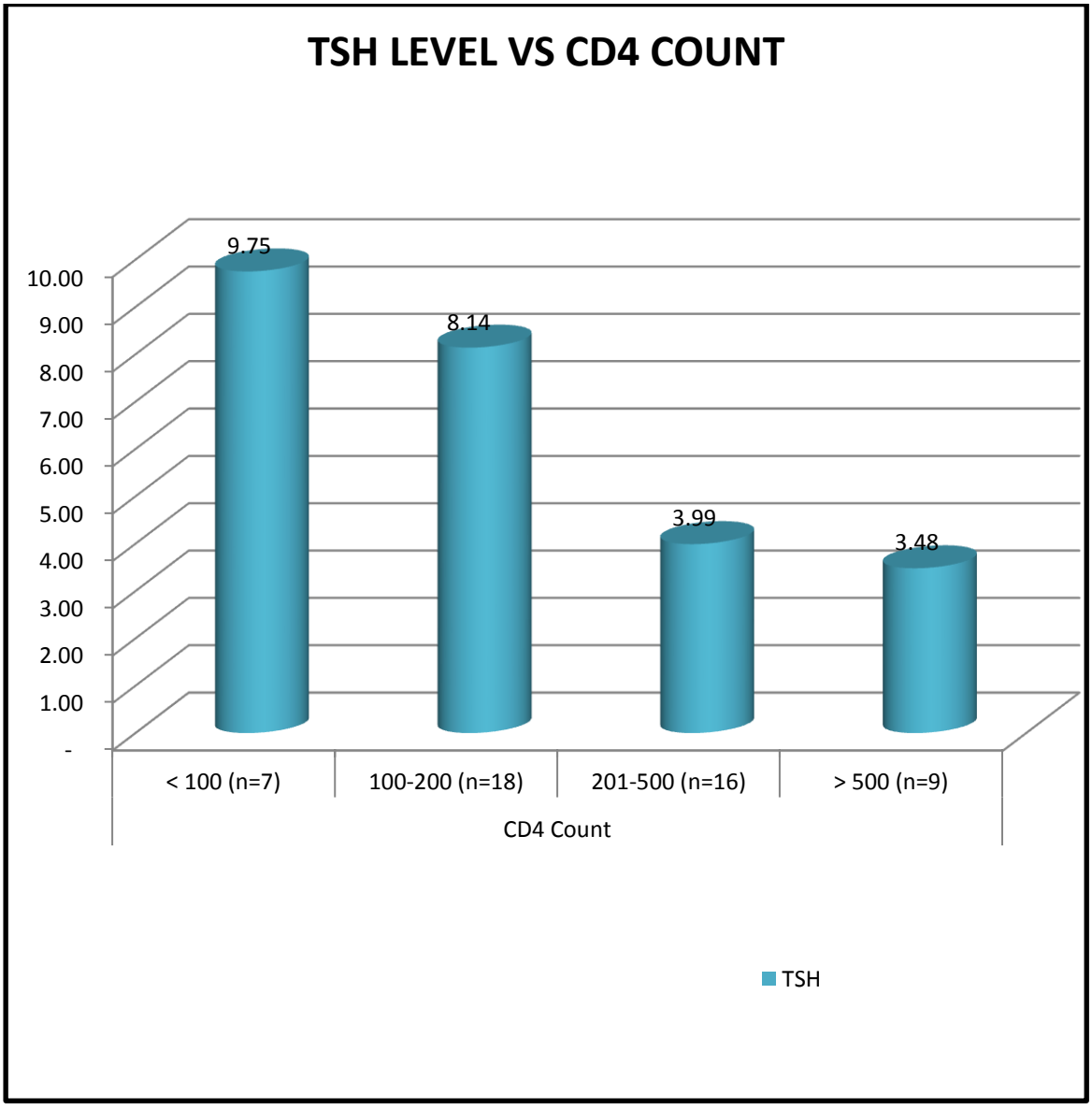


Table 6: Co relation of BMI with CD4 count

BMI(kg/m2)	CD4 Count			
	< 100 (n=7)	**100-200 (n=18)**	**201-500 (n=16)**	**> 500 (n=9)**
< 18.5	6(85.71%)	3(16.67%)	0(0)	0(0)
18.5-24.9	1(14.28%)	15(83.33%)	11(68.75)	3(33.33)
25-30	0(0)	0(0)	3(18.75)	6(66.67)
> 30	0(0)	0(0)	2(12.5)	0(0)

Figure 21: Co relation of BMI with CD4 count

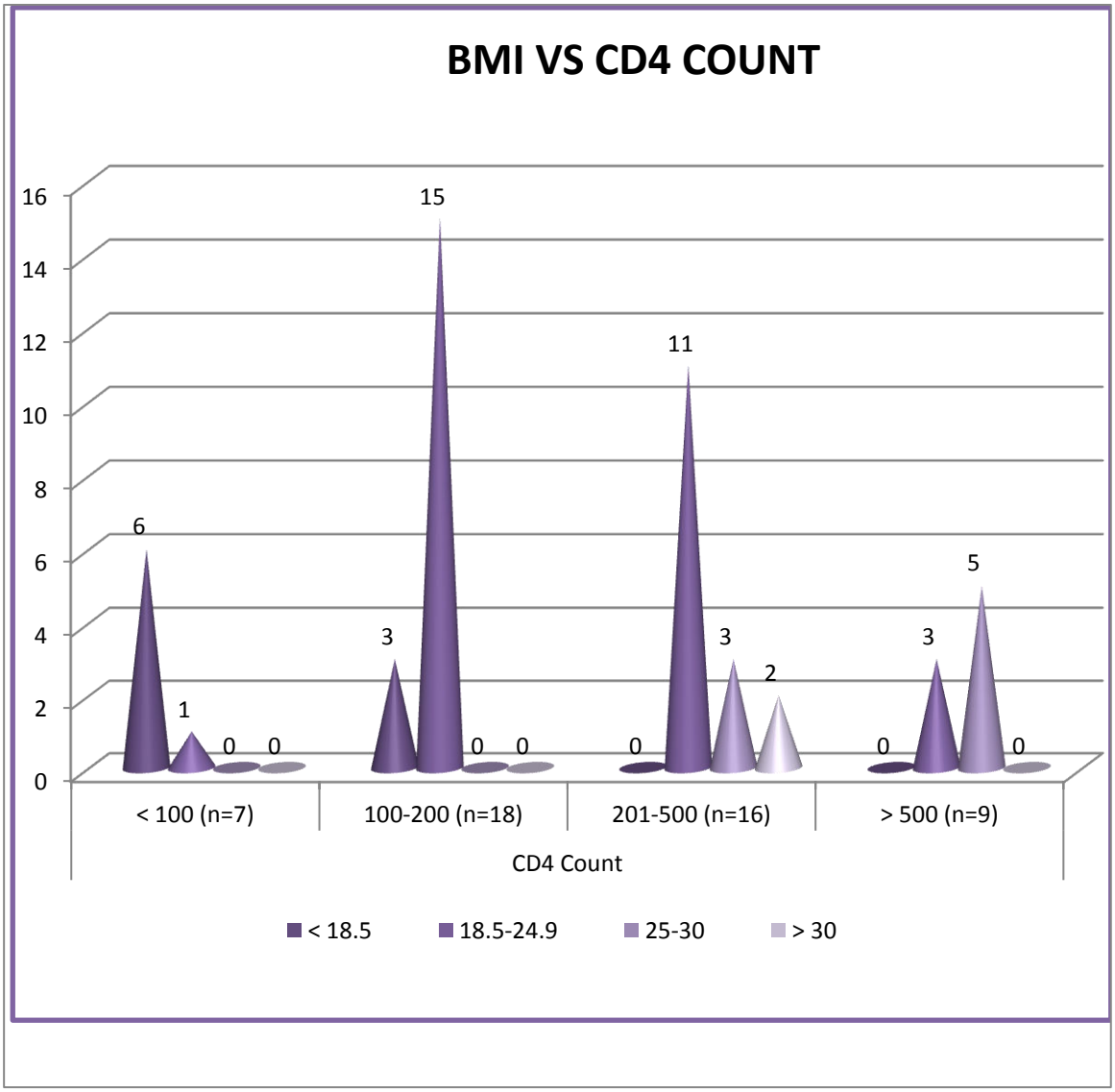
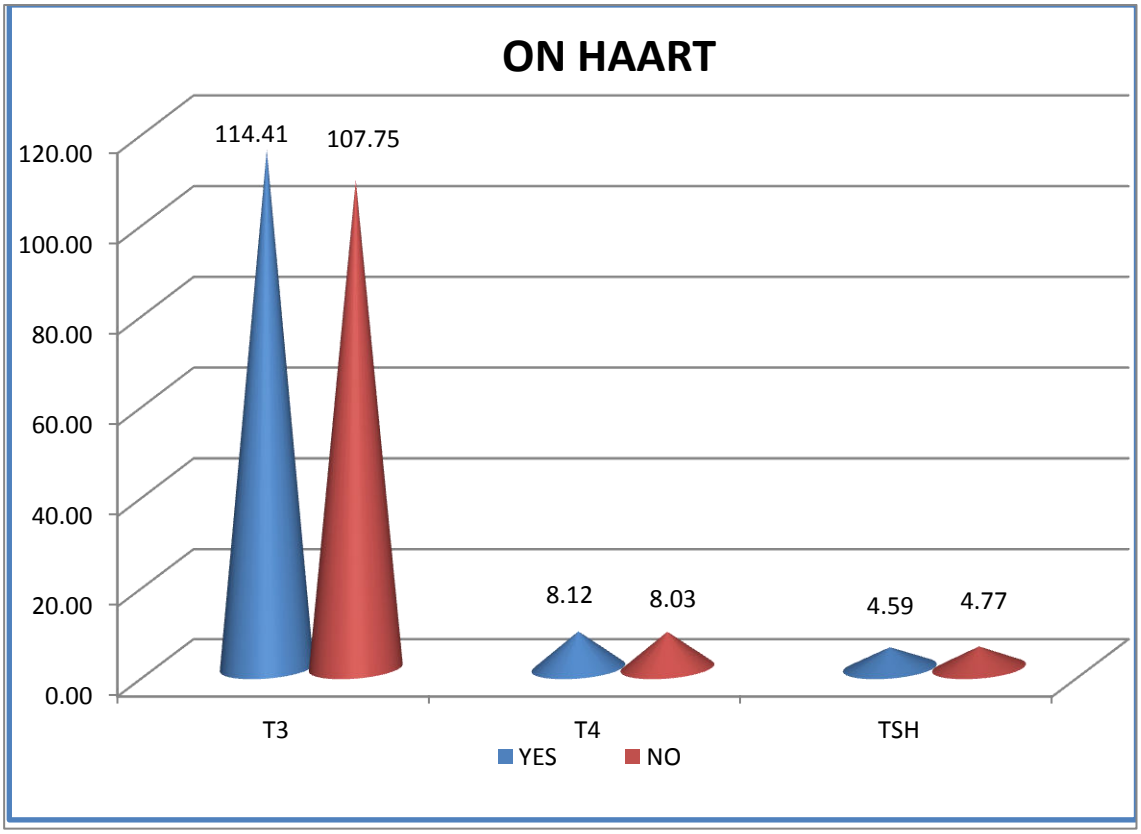


Table7: Correlation between HAART &T3, T4, & TSH

ON HAART	MEAN+S.D T3	MEAN+S.D T4	MEAN+S.D TSH
YES	120.667+26.679	8.124+2.420	4.590+1.072
NO	122.625+39.450	8.025+2.392	4.775+1.061
P'VALUE	0.861	0.916	0.657

Figure 22: Correlation between HAART &T3, T4, & TSH



DISCUSSION

We have studied the thyroid profile of50 HIV infected individuals after considering the exclusion criteria.

Out of the 50 individuals 34% were between 20-30 years of age and 40% between 31-40years. Males constituted 56% and females were 44%, however in a study done by Palaniswamy et al had 50 individuals with 100% males[8].

The thyroid profile studies in these patients revealed majority of the T3 and T4 values were in the normal range 70-190 (94%) and T4 5.0-12.0 (80%) however large portion of the TSH values were above normal range >5.0 (58%) (p=<0.001).

In a study done by Marco Bongiviani et al[20] on 35 HIV positive and Sonia Beltran et al[5]on 697 individuals showed results similar to that of ours where most of them were having a high TSH values but T3 and T4 were normal amongst these individuals.

The CD4 count in our study had a wide range of spectrum from less than 100 to more than500.When thyroid profile was co related with CD4 count it showed that people with higherCD4 count were having normal thyroid profile values than people with lower CD4 count.

Jain G et al[19] also showed that males and females were equally affected with subclinical hypothyroidism in HIV.

People with CD4 count between 100- 200 were having a mean TSH value of 8.45+/-0.32 and people with CD4 less than <100 were having TSH values 9.75+/-0.39 (p= <.001).

When CD4 was co related in males and females it showed that both males and females were affected equally with p=<.001.

A study done by Judie B alimonty[21] also showed that both males and females were having sub clinical hypothyroidism in HIV.

A low BMI was noted in individuals with a low CD4 count as compared to patients with higher CD4 counts. In a similar study done by Van Der Sande et al[23]showed that when a mean CD4 count of the population studied was taken mean CD4 of100 had BMI less than 18, mean CD4 of 160 had BMI of 16-18and mean CD4 of 290 had BMI of 19-20 however normal BMI was seen in mean CD4 above 330.

Marco Bongiviani study revealed increased prevalence of clinical hypothyroidism in both HIV individuals on HAART and those who were not on HAART[20].Collazos et al[16]found a correlation between FT4 levels and CD4 cell counts in patient treated with HAART. Majority of the patients had CD4 count >200 cells/mm^3.In our study, there is no significant correlation between thyroid dysfunction and patients on HAART.

CONCLUSIONS

1. Thyroid dysfunction is found in significant association with HIV infection and a hypothyroid state occurs in HIV infection as the disease progresses.
2. Males and females suffering from HIV show equal incidence of thyroid dysfunction.
3. All individuals with CD4 count less than 200 should be screened for hypothyroidism.
4. In individuals with a low CD4 count, a lower BMI is observed as compared to other patients with CD4 counts higher than them.
5. There is no significant correlation between thyroid dysfunction and patients treated with HAART.

SUMMARY

AIDS resulting from HIV infection may involve any organ system either directly or indirectly. Among them is the HIV related endocrinopathies that occurs during all stages of the disease, both early and late. In various studies, alterations in thyroid function tests has been analysed in HIV patients. Thyroid abnormalities are found to be more common in HIV infected patients and may be detectable even in the early phase of disease.

The changes in thyroid function tests in PLHA patients can be attributed to HIV because the prevalence is higher than the compared normal population. However TFT cannot be used as a biochemical predictor of the progression of the disease in HIVinfectionas it does not have much popularity in India. In this study an entire spectrum of HIV+ patients are screened for thyroid abnormalities ranging from asymptomatic patients to full blown AIDS.

The objective of the study was to correlate the thyroid function tests with the CD4 count in patients infected with human immunodeficiency virus (HIV) and to assess the course of thyroid dysfunction as the CD4 count further declined.

It is a prospective study involving 50 HIV infected patients at various stages of the disease. Serum T3, T4, and thyroid stimulating hormone (TSH) was done in these patients. The results were analysed and thyroid function tests abnormalities were correlated with the CD4 count and analysed statistically.

The patients included in the study were interviewed and examined for thyroid abnormalities after obtaining an informed consent.

Out of the 50 patients studied 56% were males and 44% were females. The age group ranged from 20 years to above 50 years of age. The CD4 count ranged formless than 100 to more than 500. It was seen that in 80% of the population had T4levels between 5-12.0 and 42% had TSH levels between 0.5 to 5 whereas 48% of the studied population had an increased TSH above 5. It was seen that 100% of the patients with CD4 count less than 100 had an increased TSH of above 5 and 94% of the patients with CD4 between 100-200 had TSH above 5.

It was observed that HIV patients with a low CD4 count also had a low BMI when compared to the patients with higher CD4 count. In this study it is found that thyroid dysfunction has a significant association with HIV infection and a hypothyroid state occurs in HIV infection as the disease progresses. In this study we have noted that males and females suffering from HIV show equal incidence of thyroid dysfunction. Hence we have concluded that all individuals with CD4 count less than 200should be screened for hypothyroidism.

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PROFORMA

Name:

Age/Sex/Occupation:

Presenting complaints:

H/o Fatigue, Constipation/ Diarrhoea, Cold/ Hot intolerance, Dry/ Moist skin, Hoarseness of voice, Weight gain/ loss, Menstrual disturbances, Palpitation etc.

Past history:

H/o Diabetes Mellitus, Systemic Hypertension, Drug intake altering Thyroid metabolism.

Clinical examination:

General examination:

Consciousness, Pallor, jaundice, Clubbing, Lymphadenopathy, Periorbital puffiness, Pitting pedal edema, Dry skin, Slowed speech and movements, Examination of thyroid.

Vitals: PR, BP, RR, SpO2, Temperature

Systemic examination:

CVS: RS: Abdomen: CNS:

LABORATORY INVESTIGATIONS:

1. T3, T4, TSH

2. CD4 Count

MASTER CHART

S.NO	NAME	AGE	SEX	BMI	T3	T4	TSH	CD4	RX NAIVE	ON HAART
1	KANNAN	22	M	26.1	110	6.4	2.7	684	NO	YES
2	PRAKASH	34	M	17.2	55	4.0	9.8	52	NO	YES
3	PETCHI	42	F	18.5	140	7.6	9.0	116	NO	YES
4	PANDI	52	M	30.2	112	7.1	3.5	420	NO	YES
5	RANGAN	27	M	23.7	118	9.2	5.2	238	NO	YES
6	RANI	31	F	18.7	120	11.2	8.4	132	NO	YES
7	VALLI	47	F	22.0	102	7.2	7.6	183	NO	YES
8	KALIMUTHU	25	M	24.2	108	10.5	3.5	700	NO	YES
9	MANICKAM	33	M	25.9	90	5.6	5.3	346	YES	NO
10	RAJA	41	M	17.8	92	4.2	9.6	82	NO	YES
11	GOWRI	25	F	18.1	140	7.9	7.4	176	NO	YES
12	SHANMUGAM	51	M	23.7	102	8.6	3.9	582	NO	YES
13	MOHAMMAD	28	M	26.2	141	9.2	4.2	346	NO	YES
14	PONNI	37	F	21.7	94	4.2	9.2	90	NO	YES
15	GANESAN	47	M	30.4	124	9.4	4.1	256	NO	YES
16	SEKAR	22	M	19.7	104	4.3	8.7	128	NO	YES
17	MAHARANI	31	F	19.4	118	10.4	5.2	290	NO	YES
18	PITCHAI	46	M	20.2	112	10.2	9.2	138	YES	NO
19	RASU	54	M	25.2	102	9.0	4.7	672	YES	NO
20	ARUN	20	M	19.8	134	9.1	4.3	348	NO	YES
21	TAMILSELVI	27	F	21.7	98	8.8	7.4	156	NO	YES
22	MURUGAYEE	38	F	18.4	80	3.8	9.4	86	NO	YES
23	SENTHIL	25	M	20.4	78	4.4	7.8	106	NO	YES
24	GOKILA	35	F	18	86	4.7	8.1	148	YES	NO

S.NO	NAME	AGE	SEX	BMI	T3	T4	TSH	CD4	RX NAIVE	ON HAART
25	MARUTHAM	32	F	24.2	98	11.1	7.4	170	NO	YES
26	KUMAR	39	M	25.7	110	10.9	4.0	502	NO	YES
27	RAVI	29	M	23.6	96	9.2	8.0	190	NO	YES
28	POONGODI	31	F	17.9	86	3.8	10.2	80	NO	YES
29	DHARMARAJ	46	M	26.6	102	8.5	3.8	800	NO	YES
30	NAGARAJ	51	M	24.5	116	7.9	3.5	378	NO	YES
31	SIVAPANDI	49	M	26.3	150	9.8	3.2	470	YES	NO
32	UMA	29	F	24.2	114	10.8	5.1	238	NO	YES
33	MALAR	31	F	20.9	126	10.1	4.6	270	NO	YES
34	ARUNACHALAM	35	M	23.2	132	9.5	3.0	418	NO	YES
35	VISVAM	32	M	21.7	122	11.2	2.9	582	NO	YES
36	KOTTAMMAL	26	F	19.9	146	7.1	7.6	120	NO	YES
37	RANJITHAM	37	F	21.8	154	8.3	2.7	432	NO	YES
38	JEYAM	39	M	18.2	112	3.9	7.7	116	NO	YES
39	LALITHA	42	F	21.0	144	8.9	8.2	146	YES	NO
40	VIVEK	27	M	23.5	160	11.4	3.2	486	NO	YES
41	PRIYA	35	F	18.4	142	10.7	9.6	76	NO	YES
42	NANDHINI	31	F	20.4	138	9.5	2.4	320	NO	YES
43	ANTONY	44	M	22.3	114	8.7	9.6	132	NO	YES
44	PUNITHA	25	F	25.8	104	10.6	3.2	684	YES	NO
45	SABITHA	31	F	20.2	126	9.9	4.4	296	NO	YES
46	ANBU	39	M	20.5	94	4.7	10.2	110	NO	YES
47	BHARATHI	29	F	26.4	1O5	9.1	2.6	589	NO	YES
48	MANI	36	M	22.6	116	8.5	10.1	180	NO	YES
49	YALINI	23	F	21.4	126	8.9	4.2	144	NO	YES
50	SUBBIAH	21	M	17.5	74	5.4	10.5	45	YES	NO

LIST OF ABBREVIATIONS

HIV	Human Immunodeficiency Virus
AIDS	Acquired Immunodeficiency Syndrome
PLHA	People Living With HIV and AIDS
HAART	Highly Active Antiretroviral Therapy
PCP	Pneumocystis carrnii Pneumonia
OIs	Opportunistic Infections
FDA	Food and Drug Administration
CDC	Centre for Disease Control
WHO	World Health Organisation
ELISA	Enzyme Linked Immunosorbent Assay
HTLV	Human T-Lymphotropic Virus
CD4	Cluster of Differentiation 4
MHC	Major Histocompatibility Complex
CRF	Circulating Recombinant Forms
NACO	National AIDS Control Organisation
EBV	Epstein barr virus
Tg	Thyroglobulin
TSH	Thyroid stimulating hormone

NIS	Sodium Iodide symporter
WHO	World health organization
IQ	Intelligence quotient
MIT	Mono iodotyrosine
DIT	Di iodotyrosine
TPO	Thyroid peroxidase
G-PCR	G protein coupled receptor
TBG	Thyroid binding globulin
CMV	Cytomegalovirus
TFT	Thyroid function test

Ref.No.5053/E1/5/2014

Madurai Medical College,
Maduai -20. Dated: 06 .2014.

Institutional Review Board/Independent Ethics Committee
Capt.Dr.B.Santhakumar,MD (FM). deanmdu@gmail.com
Dean, Madurai Medical College &
Government Rajaji Hospital, Madurai 625 020 . Convenor

Sub: Establishment – Madurai Medical College, Madurai-20 –
Ethics Committee Meeting – Meeting Minutes - for June 2014 –
Approved list – reg.

The Ethics Committee meeting of the Madurai Medical College, Madurai was held on 24th June 2014 at 10.00 Am to 12.00 Noon at Anaesthesia Seminar Hall at Govt. Rajaji Hospital, Madurai . The following members of the Ethics Committee have attended the meeting.

1.Dr.V.Nagarajan,M.D.,D.M(Neuro) Ph: 0452-2629629 Cell No.9843052029 nag9999@gmail.com.	Professor of Neurology (Retired) D.No.72, Vakkil New Street, Simmakkal, Madurai -1	Chairman
2.Dr.Mohan Prasad, MS.M.Ch. Cell.No.9843050822 (Oncology) drbkcmp@gmail.com	Professor & H.O.D of Surgical Oncology (Retired) D.No.32, West Avani Moola Street, Madurai.-1	Member Secretary
3. Dr.L.Santhanalakshmi, MD (Physiology) Cell No.9842593412 dr.l.santhanalakshmi@gmail.com.	Vice Principal, Prof. & H.O.D. Institute of Physiology Madurai Medical College	Member
4.Dr.K.Parameswari, MD(Pharmacology) Cell No.9994026056 drparameswari@yahoo.com.	Director of Pharmacology Madurai Medical College.	Member
5.Dr.S.Vadivel Murugan, MD., (Gen.Medicine) Cell No.9566543048 svadivelmurugan_2007@rediffmail.com.	Professor & H.O.D of Medicine Madurai Medical College	Member
6.Dr.A.Sankaramahalingam, MS., (Gen. Surgery) Cell.No.9443367312 chandrahospitalmdu@gmail.com	Professor & H.O.D. Surgery Madurai Medical College.	Member
7.Mrs.Mercy Immaculate Rubalatha, M.A., Med., Cell.No.9367792650 lathadevadoss86@gmail.com	50/5, Corporation Officer's Quarters, Gandhi Museum Road, Thamukam, Madurai-20.	Member
8.Thiru.Pala.Ramasamy, B.A.,B.L., Cell.No.9842165127 palaramasamy2011@gmail.com	Advocate, D.No.72,Palam Station Road, Sellur, Madurai-20.	Member
9.Thiru.P.K.M.Chelliah, B.A., Cell No.9894349599 pkmandco@gmail.com	Businessman, 21 Jawahar Street, Gandhi Nagar, Madurai-20.	Member

The following project was approved by the committee

Dr.A.Prabhu prabhu80kodi@gmail.com	PG in M.D., (General Medicine) Government Rajaji Hospital & Madurai Medical College, Madurai	"Prevalence of Thyroid Dysfunction in Seropositive HIV Patients"	Approved

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain it confidentially.

1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution or to Government.
2. She/He should inform the institution Ethical Committee, in case of any change of study procedure, site and investigation or guide.
3. She/He should not deviate the area of the work for which applied for Ethical clearance. She/He should inform the IEC immediately, in case of any adverse events or Serious adverse reactions.
4. She/He should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and if any Extension of time is required He/She should apply for permission again and do the work.
6. She/He should submit the summary of the work to the E thical Committee on Completion of the work.
7. She/He should not claim any funds from the institution while doing the work or on completion.
8. She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

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STUDY OF PREVALENCE OF THYROID
DYSFUNCTION IN SERONEGATIVE HIV PATIENTS

Dissertation submitted for
DOCTOR OF MEDICINE
BRANCH – I (GENERAL MEDICINE)
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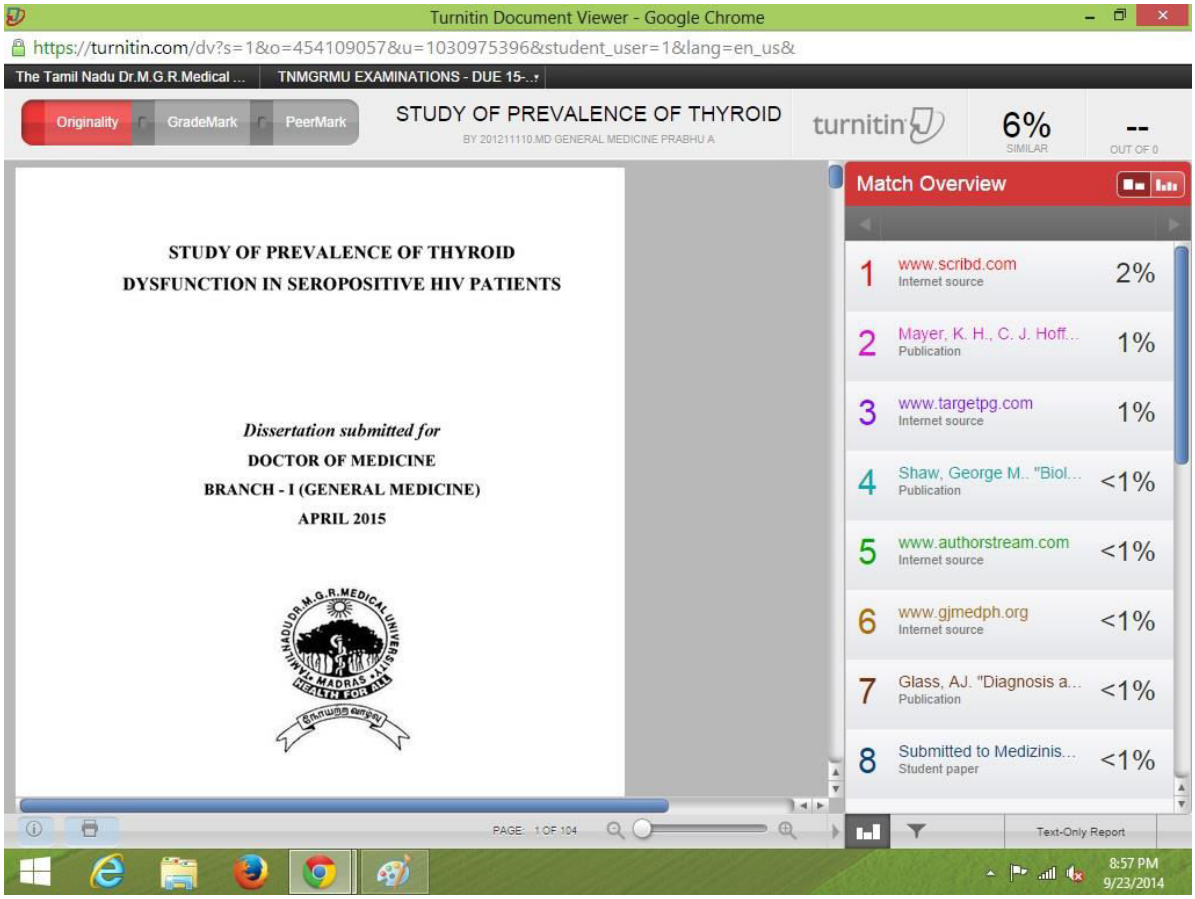
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